FOOD AND DRUG ADMINISTRATION

CENTER FOR TOBACCO PRODUCTS

TOBACCO PRODUCTS CONSTITUENTS SUBCOMMITTEE

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

TUESDAY, JUNE 8, 2010

8:30 a.m. to 5:00 p.m.

Holiday Inn

2 Montgomery Village Avenue

Gaithersburg, Maryland

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I N D E X (continued)

P R O C E E D I N G S

(8:00 a.m.)

DR. HATSUKAMI: All right. I think we'll go ahead and get started. It's 8:30 a.m., a little bit after. I'm Dorothy Hatsukami, and I'm going to be serving as the chair for this subcommittee meeting, so good morning to everyone and thank you for coming.

I think, before we get started, I'd like to have some introductions around the room, and we'll start with Dr. Ashley.

If you could just state your name and where you're from.

DR. ASHLEY: My name is David Ashley. I'm now -- I have to think about this a little bit -- director of the Office of Science of the Center for Tobacco Products at FDA.

DR. HUSTEN: And the reason David's saying that is he just started Friday.

I'm Corinne Husten. I'm senior medical advisor in the Office of the Director in the Center for Tobacco Products at FDA.

DR. HECHT: I'm Steve Hecht. I'm a

professor at the University of Minnesota.

DR. BURNS: I'm Dave Burns from the University of California San Diego.

DR. O'CONNOR: Richard O'Connor from the Roswell Park Cancer Institute in Buffalo, New York.

DR. TEMPLETON-SOMERS: Karen Templeton-Somers, acting Designated Federal Official for the committee, FDA.

DR. HENNINGFIELD: I'm Jack Henningfield, Research and Health Policy at Pinney Associates and adjunct professor in the Department of Psychiatry at the Johns Hopkins Medical School.

DR. WATSON: I'm Cliff Watson. I'm with the Centers for Disease Control and Prevention in Atlanta, Georgia.

DR. DJORDJEVIC: I'm Mirjana Djordjevic, and I'm at the Tobacco Control Research Branch of the National Cancer Institute.

DR. FARONE: I'm Bill Farone, president and CEO of Applied Power Concepts, Incorporated.

DR. LAUTERBACH: I'm John Lauterbach, owner and principal, Lauterbach & Associates, Macon, Georgia, consultants in chemistry and toxicology of tobacco. And I'm here representing the interests of the small business tobacco manufacturers.

DR. HECK: I am Dan Heck, a principal scientist at the Lorillard Tobacco Company, and I'm here representing the tobacco industry.

DR. HATSUKAMI: Thank you. Now, I want to just make a few statements and so I have to read this verbatim.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly felt, or held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruptions. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topics at hand take place in the open forum of the meeting. We are aware that members of the meeting are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

DR. TEMPLETON-SOMERS: Good morning. I would first like to remind everyone present to please silence your cell phones if you have not already done so. And I would also like to identify today's FDA press contact, Tesfa Alexander. Tesfa's over on the side there. And I'd like to read the conflict of interest meeting statement.

The Food and Drug Administration is convening today's meeting of the Tobacco Product Constituent Subcommittee of the Tobacco Product Scientific Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry

representative, all members and consultants are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of this subommittee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that the members and consultants of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential conflicts of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves receiving presentations and discussing the development of a list of harmful or potentially harmful constituents, including smoke constituents, in tobacco products. Topics for discussion will include the criteria for the selection of the constituents; developing a proposed list of harmful or potentially harmful constituents; the rationale for including each constituent; and the acceptable analytical methods for assessing the quantity of each constituent.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and consultants, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and consultants to disclose any public statements that they have made concerning the issues before the committee.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Daniel Heck and John Lauterbach are participating in this meeting as nonvoting industry representatives, acting on behalf of the interests of the tobacco manufacturing industry and the small business tobacco manufacturing industry, respectively. Their role at the meeting is to represent these industries in general and not any particular company. Dr. Heck is employed by Lorillard Tobacco Company and Dr.

Lauterbach is employed by Lauterbach & Associates, LLC.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. HATSUKAMI: I think we'll go ahead and get going with the first presentation. It's going to be given by Dr. Corinne Husten, and she will be giving the charge to the committee.

DR. HUSTEN: Good morning. I'd like to welcome the members of the committee, TPSAC Committee, who are here as well as the consultants who are here to help us with this issue. The topic of this subcommittee meeting is on harmful and potentially harmful constituents in tobacco products and tobacco smoke.

First I want to talk about what's required under the Tobacco Control Act on this issue. So the Tobacco Control Act states that FDA shall establish and periodically revise, as appropriate, a list of harmful and potentially harmful constituents, including smoke constituents, to health.

There are some definitions in the statute. There is no specified definition of constituent, but there is a definition of smoke constituent. And that is any chemical or chemical compound in mainstream or sidestream tobacco smoke that either transfers from any component of the cigarette to the smoke or that is formed by the combustion or heating of tobacco, additives, or other components of the tobacco product.

I'm going to be, on the slides, abbreviating harmful and potentially harmful constituents as H/PH in the interests of having the slides be a little less dense.

So as a point of information only, I want to let you know, because it's relevant to this committee, that we have published a draft guidance on harmful and potentially harmful constituents in tobacco products. It is a draft guidance; it's not for implementation. It's being issued now so that we can get public comments.

There will be a Federal Register notice coming out shortly that will give the specific instructions about how to send those comments in, and we welcome, obviously, comments from everyone. But I wanted to let everybody know what this draft guidance says.

So it says, "For the purpose of establishing a list of harmful and potentially harmful constituents, including smoke constituents, to health in each tobacco product by brand and by quantity in each brand and sub-brand is required under Section 904(e) of the Act.

"FDA believes that the phrase 'harmful and potentially harmful constituent' includes any chemical or chemical compound in a tobacco product or in tobacco smoke that is, or potentially is, inhaled, ingested, or absorbed into the body and that causes or has the potential to cause direct or indirect harm to users or nonusers of tobacco products.

"Examples of constituents that have the potential to cause direct harm to users or nonusers of tobacco products includes constituents that are toxicants, carcinogens, and addictive chemicals and chemical compounds.

"Examples of constituents that have the potential to cause indirect harm to users or nonusers of tobacco products include constituents that may increase the exposure to the harmful effects of a tobacco product constituent by, 1) potentially facilitating initiation of the use of tobacco products; 2) potentially impeding cessation of the use of tobacco products; or 3) potentially increasing the intensity of tobacco product use, such as the frequency of use, amount consumed, depth of inhalation.

"Another example of a constituent that has the potential to cause indirect harm is a constituent that may enhance the harmful effects of a tobacco product constituent."

So the purpose of this subcommittee, in two subcommittee meetings, we would like the subcommittee to review the example lists of harmful and potentially harmful constituents that have been developed by other countries; identify which chemicals or chemical compounds are appropriate for an initial FDA list of harmful and potentially harmful constituents; identify established methods for measuring each constituent on the initial list; and identify other potentially important information or criteria for measuring the harmful and potentially harmful constituents on the initial list.

I do want to point out that subcommittees make preliminary recommendations to the full advisory committee regarding specific issues, and the full committee will deliberate on the recommendations from the subcommittee and make the final recommendations to the agency on these issues.

So the questions for this particular meeting are, first, what criteria do you recommend to the advisory committee for selecting the harmful and potentially harmful constituents in tobacco products or tobacco smoke, and the criteria then will be used for developing the initial list?

Two, what harmful and potentially harmful constituents do you recommend to the advisory committee be included on the initial FDA list, and how do these meet the criteria?

And, three, what established analytical

methods do you recommend to the advisory committee for assisting the quantity of each harmful and potentially harmful constituent in tobacco products or tobacco smoke?

So I do want to lay out some parameters for this first meeting. FDA requests that the subcommittee focus on the harmful and potentially harmful constituents that are potentially ingested, absorbed, or inhaled -- that is, absorbed from the product itself or combustion products that are inhaled -- and focus on chemical and chemical compounds that are toxicants, carcinogens, or addictive.

FDA requests that the subcommittee identify the criteria that the subcommittee will use for determining whether a constituent is a carcinogenic, toxicant, or addictive chemical or chemical compound that you recommend to be included on the harmful and potentially harmful list.

Identify constituents from the example, WHO, and country lists, that you recommend for the initial FDA harmful and potentially harmful constituent list.

We do note that different countries may use the term "constituent" differently, but we ask that the subcommittee have a consistent approach.

We ask that the subcommittee reviews the information from the additional example lists of harmful and potentially harmful constituents that have been developed by various organizations to identify harmful and potentially harmful constituents that may be missing from the example, WHO, and country lists.

FDA requests that the subcommittee identify established analytical methods for assessing the quantity of each harmful and potentially harmful constituent in tobacco products or tobacco smoke. We would like you to focus first on whether measures to assess the quantities of each harmful or potentially harmful constituent exist, such as mass spectrometry, but leave a detailed discussion of the methods until after all of the initial questions have been answered.

Again, we'd like to point out that there may be more than one established method for a particular constituent, and when this is the case, the subcommittee does not need to identify a single method.

I do have three points of clarification. Asking the subcommittee to focus on carcinogens, toxicants, and addictive chemicals or chemical compounds does not imply that FDA will not be reviewing other chemicals or chemical compounds for possible inclusion on the harmful and potentially harmful constituent list.

Second, providing information to the subcommittee on the four disease outcomes of cancer, cardiovascular disease, respiratory effects, and addiction does not imply that FDA will not be reviewing other disease outcomes for assessing chemicals or chemical compounds for possible inclusion on the harmful and potentially harmful constituent list.

FDA recognizes that harmful and potentially harmful constituents in smokeless tobacco may be underrepresented on the example country lists and other organizations' lists, and the request to use these example lists as a starting point for the subcommittee's discussion does not imply that FDA will not be reviewing other chemicals or chemical compounds in smokeless tobacco for possible inclusion on the harmful and potentially harmful constituent list.

So to recap, the questions to the subcommittee for this meeting are, what criteria do you recommend to the advisory committee for selecting the harmful and potentially harmful constituents in tobacco products or tobacco smoke, and which will be used to develop the initial list; what harmful and potentially harmful constituents do you recommend to the advisory committee be included on the initial FDA list, and how do they meet the criteria; and, three, what established analytical methods do you recommend to the advisory committee for assessing the quantity of each harmful and potentially harmful constituent in tobacco products or tobacco smoke?

Are there any clarifying questions?

DR. LAUTERBACH: I have three clarifying questions. The first concerns the WHO report that was included in the briefing material.

Why are we limiting ourselves to a biased document that has not been fully peer-reviewed and that is coming from other countries, not from our own chemistry and toxicology understanding of tobacco and tobacco smoke?

DR. HUSTEN: Our purpose was to include example lists that other countries or organizations have used when thinking about these constituents in terms of reporting or regulatory requirements. Including the list is not conferring any kind of judgment on the list; they are example lists.

DR. LAUTERBACH: The second question here. The briefing materials I received were very deficient in anything dealing with methodology or recent journal articles on methodology that appeared in the peer-reviewed literature.

Is there a reason for that?

DR. HUSTEN: Yes. As you noted in my comments, we are requesting for this initial meeting that the committee focus on potentially harmful -- harmful and potentially harmful -- sorry, that's a mouthful -- constituents and just whether methods exist, and to leave the details of the methods until the next meeting. And so the background materials for the next meeting will have more detailed information about methods.

DR. HATSUKAMI: Dr. Lauterbach?

DR. LAUTERBACH: One final question. The compounds you claim that are addictive compounds that increase the addictiveness of tobacco or tobacco smoke in use, could you please identify some of those in your literature references, please?

DR. HUSTEN: Discussion of the specific constituents will be in the next presentation.

DR. HATSUKAMI: Dr. Burns?

DR. BURNS: I just wanted to sort of clarify the mechanisms by which we can include things. There's lots of different compounds, and if we are going to have to develop our own individual criteria for putting compounds on that hazardous list, that will be a formidable intellectual exercise, an exercise that many other organizations have already gone through to develop criteria.

So one of the questions I have to ask about format is can we simply -- or not simply -- can we examine the criteria used by other organizations and discuss the appropriateness of those criteria and consider adopting them rather than building, from ground zero, a new set of criteria?

DR. HUSTEN: Yes, you can.

DR. HATSUKAMI: Any other questions from the group?

[No response.]

DR. HATSUKAMI: Thank you.

Our next presentation will be given by Dr. Patricia Richter from the Centers for Disease Control.

DR. RICHTER: Good morning. I'm Patricia Richter with the Office on Smoking and Health at the Centers for Disease Control and Prevention. And this morning I'll be discussing example lists of harmful and potentially harmful constituents in tobacco products and tobacco smoke.

For this presentation, I'll begin by reviewing relevant terms and concepts, provide a brief summary of entities requiring or considering requiring constituent reporting, give an overview of examples of lists of harmful and potentially harmful constituents, and end with clarifying questions.

For the purpose of this presentation, cigarette smoke is the smoke produced by the incomplete combustion of a tobacco cigarette. It's typically described as an aerosol composed of liquid droplets in a gas phase, and it has been said that it contains more than 5,000 identified constituents.

Mainstream smoke is the smoke generated during active puffing and the smoke drawn into a smoker's mouth. Mainstream smoke is also the portion of smoke exhaled by a smoker that becomes a component of secondhand smoke.

Sidestream smoke is the smoke generated between puffs and when a cigarette smolders, and sidestream smoke is sometimes used as a surrogate for secondhand smoke.

Particularly relevant to this presentation are what is known as the Hoffmann analytes or the Hoffmann lists. And while the actual number of chemicals referred to as Hoffmann analytes may vary, it is typically a list of 44 chemicals and chemical mixtures.

The Hoffmann analyte list is considered a summary of toxic and carcinogenic chemicals present in mainstream cigarette smoke. And the Hoffmann analyte list is attributed to lists and publications authored by Dr. Dietrich Hoffmann, then with the American Health Foundation. And the Hoffmann analyte list has been used by several countries and organizations when developing their constituent lists.

In this presentation, I'll briefly review information from the World Health Organization, Brazil, Canada, Australia, and New Zealand. For consistency, I'm using the term "constituent," however, alternate terms or definitions may have been used by other countries. It's also important to note that the lists used in this summary may have been developed with different rationales.

Article 9 of the Framework Convention on Tobacco Control of the World Health Organization states that, "The conference of parties shall propose guidelines for testing and measuring the contents and emissions of tobacco products, and for the regulation of these contents and emissions."

The WHO Study Group on Tobacco Product Regulation prepared a technical report that included an assessment of toxicants. This assessment considered annual and human toxicity data with special note to cardiovascular and pulmonary toxicity and carcinogenicity, toxicity indices, variation in toxicants across brands, the potential for the toxicant to be lowered. It looked for representation across both particulate and gas phase constituents, and from the different chemical classes known to be present in cigarette smoke.

The authors of the report arrived at 18 mainstream smoke constituents. They termed seven of the 18 constituents most hazardous, and they used the Hoffmann analyte list to develop this provisional list of cigarette constituents for product regulation.

In Brazil, the National Health Monitoring Agency is responsible for administering the constituent reporting in their country. Details of their program are provided in the RDC Resolution Number 90, published in 2007, which describes the process for registration of smoking products derived from tobacco. The process is mandatory for all brands of smoking products derived from tobacco, and analytical and reporting formats are specified.

In Brazil, constituent reporting consists of 27 tobacco constituents, 45 mainstream smoke constituents, and 44 sidestream smoke constituents, and the Hoffmann analyte list served as the basis for their constituent list.

In Canada, Health Canada is responsible for administering the tobacco reporting regulations published in 2000, which provides for requirements for the reporting of toxicant constituents and toxic emissions. Constituent reporting is required for a variety of tobacco products, including cigarettes, cigarette tobacco, leaf tobacco, tobacco sticks, kreteks, and bidis, and as with Brazil, analytical and reporting formats are specified.

In Canada, constituent reporting is required for 26 tobacco constituents, 39 mainstream smoke constituents, and 38 sidestream smoke constituents. And as with Brazil, the Hoffmann analyte list served as a basis for their constituent reporting list.

In Australia, there is not an official list of constituents. However, in 2001, three tobacco manufacturers voluntarily provided cigarette smoke chemistry data for a selection of Australian cigarette brands. This report to the Australian Department of Health and Ageing contained data for 37 mainstream smoke constituents, and the data for the 37 mainstream smoke constituents is incorporated in the WHO technical report as providing evidence of variation in levels of constituents across brands within countries.

In New Zealand, the New Zealand Ministry of Health is responsible for administering the Smoke-Free Environments Act of 1990, which requires manufacturers to report annually the tar and nicotine yields in the smoke of manufactured cigarette brands.

After enactment of the Smoke-Free Environments Act, the Ministry of Health adopted a harm reduction approach for tobacco products, and in 1997 the New Zealand parliament amended the Smoke-Free Environments Act to clarify regulatory powers to limit harmful constituents in tobacco products. To this end, a report was prepared in 2000 by the

Environmental Health Effects Program of the Environmental Science and Research Institute for the New Zealand Ministry of Health.

The authors of the report describe a risk-based priority-setting scheme for cigarette harm reduction. They begin with approximately 95 chemicals in cigarette smoke, and employ a risk assessment model that incorporates mainstream and sidestream smoke data, cancer potency factors, and non-cancer health effects potency data, for a variety of health endpoints. The authors of the report arrive at 16 mainstream smoke constituents, 14 sidestream smoke constituents, and they recommend that ammonia and NNK be included.

Looking across these five lists, in summary, there are 59 chemicals and chemical mixtures, 48 mainstream smoke constituents, 46 sidestream smoke constituents, and 27 tobacco or tobacco product constituents, and 20 constituents are common to four or more lists. There is limited information on the rationale for the constituents being on the list, so we looked at potential associations with known tobacco-related diseases.

Among the 59 constituents, 32 constituents may play a role in smoking-related cancers. Based on classifications by the International Agency for Research on Cancer, the National Toxicology program, the Environmental Protection Agency, and reports in the peer-reviewed literature, 26 of the 59 constituents are known, probable, or possible human carcinogens or tumor promoters.

Among the 59 constituents, there are 12 known human carcinogens based on NTP or IARC classifications, 2-aminonaphthalene, 4-aminobiphenyl, arsenic, benzene, benzpyrene, 1,3-butadiene, cadmium, chlorinated dioxin, chromium, nickel, and two tobacco-specific nitrosamines, NNK and NNN.

Among the 59 constituents, at least 24 are potentially toxic to the respiratory system. Based on reports in the peer-reviewed literature, almost 60 percent have the potential to act as irritants to the eye and respiratory tract, and several have been tested in laboratory studies and have been shown to be toxic to the ciliated cells of the lungs. Volatile aldehydes and hydrogen cyanide have been indicated as probable causative agents in the chronic obstructive pulmonary disease seen amongst smokers.

Among the 59 constituents, at least 17 have demonstrated toxicity to one or more components of the cardiovascular system. For example, exposure to poly-aromatic hydrocarbons or cadmium is associated with increased risk of development of atherosclerosis or peripheral artery disease. Exposure to lead and volatile aldehydes is associated with increased risk of elevated blood pressure. And carbon monoxide and nitrogen dioxide are two examples of constituents which may reduce the oxygen-carrying capacity of the blood.

In addition to nicotine among the constituents, at least five others may contribute to tobacco addiction. For example, acetaldehyde has been shown to have reinforcing effects in rodents, and the minor tobacco alkaloids are reported to be pharmacologically active.

Of the remaining constituents on the list, there are eight -- glycerol, menthol, nitrate, propylene glycol, sodium propionate, sorbic acid, triacetin, and triethylene glycol -- for which the association with smoking-related disease remains to be determined. However, it is possible that they are present on one or more constituent lists because some may generate hazardous combustion products when burned; for example, carbon monoxide and reactive aldehydes. And in the case of nitrate, levels of nitrate in the tobacco serve as a precursor for the formation of tobacco-specific nitrosamines in smoke.

This concludes this summary presentation. I'll take clarifying questions.

DR. HATSUKAMI: Yes, Dr. Lauterbach?

DR. LAUTERBACH: Yes. Dr. Richter, you mentioned that several countries have established these lists, have required constituent reporting.

Can you please tell us what those governments have done with those data that they have received? Have compounds been banned? Have products been banned? Have products been removed from the market, or have manufacturers been forced to modify their products?

I mean, how is all these data, such as Canada, Brazil -- how has all those data been used in terms of improving public health?

DR. RICHTER: I think that that's outside the scope of this presentation. This presentation looked at the examination of constituents that they include in their constituent reporting process.

DR. HATSUKAMI: Yes, Dr. Burns?

DR. BURNS: Just a clarification on the WHO report. There were actually nine constituents identified as high risk. They included the ones that had been included in a previous report, which are NNN and NNK, and they didn't want to get into trouble by leaving them out.

The second is that the selection of those was not based exclusively on their toxicity. It really was based on the criteria that you outlined, and it was done for purposes of making recommendations for regulation rather than for exclusively making recommendations based on its toxicity per se.

DR. HATSUKAMI: Mirjana?

DR. DJORDJEVIC: There is inconsistency in reporting the number of constituents in tobacco smoke. The old information was around 5,000. But after the publication by Rodgman and Perfetti, we are now talking about 8,000 constituents in tobacco, and almost the same number in tobacco smoke. So that should be kind of clarified, and we should from this point go with one number instead of going back and forth.

DR. HATSUKAMI: Any other questions? Yes, Dr. Lanier?

DR. LAUTERBACH: Yes. Dr. Richter, you mentioned acetaldehyde up there as modifying the properties of smoke.

Could you please go into some more detail on that?

DR. RICHTER: I mentioned that acetaldehyde is thought to contribute to the addictive properties of tobacco smoke. And it has been shown in at least one study to have reinforcing effects in rodents and to act in concert with nicotine.

DR. HATSUKAMI: Dr. Farone?

DR. FARONE: Yes. I'd just like to -- there are other lists, of course; for example, the California list of carcinogens and things which are harmful to health. And along with a comment made by Dr. Burns, I would imagine that using some of the information or criteria on those lists would also be a part of something we could look at as part of the deliberations.

DR. HUSTEN: Yes. We had chosen lists that were very specific for being both in tobacco products or tobacco smoke. But obviously, there are other lists that may include some of these chemicals or chemical compounds, and rationales that were used on other lists can be used.

DR. HATSUKAMI: Dr. Burns?

DR. BURNS: I just had other comment on language. The carcinogens have been identified with animal studies, largely of end organ carcinogen cancers that actually occur, or at least organ system changes that have occurred. Many of the other compounds that are being listed are listed as cardiovascular or chronic obstructive lung disease.

I'd make a plea that we don't do that

because that implies that the criteria we're going to use requires a demonstration of end organ cardiovascular disease or end organ chronic obstructive lung disease in order to be included in that list; whereas I think we would be better off examining the actual outcomes that were measured in the study, such as inflammation or oxidative stress or some of the other actual outcomes that are measured in the analyses rather than defining them in relation to their organ system.

We can then link those mechanisms to the organ system, such as inflammation and chronic lung disease, without having to demonstrate that a specific compound has been taken to the point of human chronic obstructive lung disease demonstration or even animal chronic obstructive lung disease demonstration.

If we don't do that, then I think we're limiting ourselves by the absence of adequate animal models for lung disease and heart disease for individual chemical constituents.

DR. HATSUKAMI: Yes, Dr. Watson?

DR. WATSON: I'd just like to reinforce

something that Corinne Husten mentioned this morning, that these lists appear to me that really do focus mainly on cigarette smoke, and that I think smokeless products are underrepresented on these lists.

I want everyone to think in the back of their mind about that and keep that in mind when they're thinking about the lists; and also maybe get some clarification. One doesn't want to come up with some sort of master list that one size fits all. There might be some things in one product -- smokeless, for instance -- where you don't necessarily need or it wouldn't make sense to measure in mainstream smoke.

So I don't know if we can make recommendations to the committee for different classes of products. There might be different subsets we want to look at. But I'd appreciate any feedback that we can get here.

DR. HATSUKAMI: Dr. Lauterbach?

DR. LAUTERBACH: Just one thing with respect to what Dr. Burns just said. It almost sounds like he's looking to add compounds, or even go to biological markers instead of the list Dr. Richter proposed.

Is that correct?

DR. BURNS: No. I'm just proposing that we be clear on the terminology we're using for including things on the list. If we are going to list chronic obstructive lung disease, then we need to have chronic obstructive lung disease as a defined outcome in the assessment of those particular chemicals. That's not commonly done for most of the agents that induce inflammation that are thought to contribute to chronic lung disease.

So if we are clear -- that is, we define the outcomes that actually occur as the criteria for inclusion or exclusion -- then there won't be any question as to what we're actually saying.

DR. HATSUKAMI: Dr. Henningfield, did you have something?

[Dr. Henningfield shakes head negatively.]

DR. HATSUKAMI: One of my questions that I have is one of the charges that we have is to actually specify the criteria by which we will choose these harmful and potentially harmful constituents. And I was wondering if you can clarify what types of criteria these different countries had used to select their constituents.

DR. RICHTER: I think the WHO report provides the most detailed description of their process. Also, the report prepared in New Zealand, although it's not an official list, that also describes their process, where they used a harm reduction. That was their goal.

The other two countries, Brazil and Canada, there wasn't as much information available on the rationale for the selection of the constituents. I think that they were probably working closely in concert with the ability to analyze the chemicals in smoke. But that's just my supposition. And that was basically what drove us to look, then, possibly at the potential association with tobacco disease.

If you go back and you look at the Hoffmann analyte list that had been published in the past, there has been an attempt over time to kind of justify one as a carcinogen or one as a tumor-promoter or one as a toxicant, and that has provided for that Hoffmann analyte list.

Then, of course, some of these lists go beyond, and you have to just kind of look at the toxicity that's known for the chemical and put it in the context of tobacco exposure to try to develop a rationale.

DR. HATSUKAMI: Any other clarifying questions?

[No response.]

DR. HATSUKAMI: Thank you.

I think what we'll do is we'll take a quick break. We're way ahead of schedule. And so I think we'll take a quick 15-minute break to set up for the next presentation, which will be the presentation from the industry.

So let's take a 15-minute break, and then we'll go from there.

(Whereupon, a recess was taken.)

DR. HATSUKAMI: Our next set of presentations is from the industry, and the first presenter is Dr. Michael Ogden from R.J. Reynolds

Tobacco Company.

DR. OGDEN: Thank you, Madam Chairman. Good morning, ladies and gentlemen. I'm Mike Ogden of R.J. Reynolds Tobacco Company, and I work in the Regulatory Oversight department, whether I hold the title of senior director.

A few preliminary points to make about this presentation. I am speaking from a composite list of slides that were created by a number of individuals. So if we move to the third point on this slide, as requested by the FDA, representatives of multiple individual tobacco manufacturers contributed to this slide deck. I'll show you the attribution of that in just a moment.

Some individual manufacturers have submitted their own written comments to these proceedings. And after this presentation, during the clarifying questions, I will certainly be here to answer questions on behalf of my employer, R.J. Reynolds, but there are also representatives of other individual tobacco product manufacturers who will be available to provide their perspectives. They are seated inside the ropes over here, Dr. Jane Lewis of Altria Client Services and Dr. Bill True of Lorillard Tobacco Company.

The contributors to this presentation are itemized on this slide, and I'll just read through them for the transcript, perhaps.

Altria Client Services, on behalf of Philip Morris USA and U.S. Smokeless Tobacco; Commonwealth Brands; Japan Tobacco International; King Maker Marketing; Liggett Group; Lorillard Tobacco; R.J. Reynolds, on behalf of itself; and American Snuff Company; Lane Limited; R.J. Reynolds Tobacco CI Company, which is our Puerto Rican company; Santa Fe Natural Tobacco; Swedish Match North America; and Vector Tobacco.

By way of an overview, I'd just like to walk through the basic educations of this talk. It's scheduled for about an hour. I hope we can do it in that period of time. I trust we can.

I'm going to give a brief indication, and certainly then talk about some background information that is related to primarily sources of tobacco and finished product variability; then talk about some fundamental considerations, primarily what is the purpose of identifying or establishing a list of harmful constituents.

We'll then move into some considerations for scientific framework for selecting individual constituents -- there was some of that discussion you heard this morning in the first presentation; then talk a bit about testing methods, particularly methodological considerations, and give an historical perspective of smoke testing over the last decade or so.

First and foremost, a clear purpose for developing a list of harmful and potentially harmful constituents is absolutely critical because only once the list is established and determined to be fit for purpose will it be able to adequately inform product characteristics and also, ultimately, public health.

I want to stress that tobacco is an agricultural product. Tobacco is grown in dirt. It's cured in barns. It's not a pharmaceutical product. Tobacco and smoke constituents are thus subject to inherent variability, and I will point out some of the more obvious causes for tobacco and constituent variability.

The framework for developing a list of harmful and potentially harmful constituents needs to be science-based. We've heard this. We've heard Dr. Deyton speak a number of times, and that's always been a point that he's focused on is the Center for Tobacco Products, its deliberations, this committee will focus on science. I personally think this is an excellent opportunity for the center and the advisory committee to do just that, focus on sound science.

Then finally, any testing or reporting of constituents that may ultimately derive from such a list has to be based on properly standardized methodologies that are fit for purpose. Without that, there's a lot of data generated, but not much information.

So by way of background, we'll walk through some issues around tobacco variability. As I've said, tobacco is an agricultural product. I will talk about constituents; you may see there in the footnote of the slide I've defined constituents as chemicals appearing in tobacco or smoke, which is very similar, I think, to the definition that was shown you this morning around the draft guidance that was issued late last week.

There is inherent variability. There certainly is the potential impact at the farm level, depending on what is done with constituent information, and because, as I will show you some of the farm-level variability sources, I think it's easy to imagine how trying to move around constituents in the tobacco leaf may in fact impact the farm.

Constituents in smoke, absolute and relative smoke yields, depend on a number of variables. We'll talk about a few of those. And I would like to point out that, which our research and others have shown, that oftentimes a reduction of one constituent in a complex mixture often results in an elevation of another, or another class of compounds.

A little bit of a classification exercise. Most of the commercial tobaccos that are produced in the world are nicotiana tabacum. It's an interesting tidbit, I thought, that looking at the tobacco genome initiative at North Carolina State University, they've estimated that the size of N. tabacum genome is 4.5 billion base pairs, which is actually larger than the human genome.

There are a number of properties of tobacco that dictate their usabilities for finished products. I've listed a few here, and I will go into those in a bit more detail on the next slide.

Some of those sources of tobacco variability include, obviously, the tobacco variety -- I'll give you some numbers on the number of varieties in commercial production in a few minutes. The leaf stalk position, which is something many people don't realize, is that the lower stalk positions and the upper stalk positions, there are chemical differences. Certainly there are differences in the nicotine content of the leaf.

It makes a difference as to how closely together the plants are grown. Certainly the growing region of the world makes a difference in terms of soil conditions. And obviously, the last point about weather and climatic conditions, from year to year and also from region to region, make tremendous and measurable differences in the tobacco leaf. Other agronomic practices such as application of fertilizer, crop protection agents, and other things certainly have impact as well.

I'll show you a couple of pictures there. The top one, actually, is just north of my hometown of Winston-Salem, North Carolina. You can see flue-cured tobacco growing in the field, and you can see our local landmark, Pilot Mountain, just to the north of Winston Salem.

Field practices are also important, potential contributors to constituents on or in the tobacco. Like most agricultural crops, tobacco plants are affected by seedling quality, plant populations, plant/water relationships, and certainly climatic factors.

There are special requirements for commercially grown tobacco such as topping, which is removing the flowering top of the tobacco as it grows; and removing the suckers, which are the axillary bud growths that come out at the junction of the stem and the stalk. And, as I pointed out earlier, quality and composition varies, certainly, with position on the plant stalk.

I'll turn now to curing practices. Certainly the type of curing that is applied to fresh green tobacco leaf impacts its chemical and thus sensory qualities as well. The two major curing methods are what are called flue curing and air curing, and they provide quite different results, even if the same plant variety is used to hang in the barns.

During the curing process, which includes aging and fermentation, there are other chemical processes that occur that are organoleptically important; that is, they contribute to the sensory experience, or the taste, of tobacco.

I've got a few pictures there. The top one on the right, on your right, is a flue-curing tobacco barn in South Carolina. The middle one is an air-curing barn in Kentucky. And the bottom one is a sun-curing operation, presumably somewhere in the eastern

Mediterranean, perhaps Turkey or Greece.

Another issue of tobacco variability is the storage practice because freshly cured tobacco leaf is not ready for us immediately. Cured tobacco is typically stored for several years. You can see an example picture at the bottom, where large bales of tobacco are in a warehouse being stored. The duration policies of tobacco storage vary from company to company, but it is measured in years, not in months, typically, and additional chemical changes occur as the tobacco ages.

A typical American blended cigarette usually contains a mixture of several types of tobacco and processed tobacco. Certainly flue-cured tobacco, which is also known as Virginia or bright tobacco, is a major component of American blend cigarettes, as is burley tobacco, which is an air-cured tobacco. Oriental or Turkish tobacco, which is a sun-cured tobacco, is an important ingredient of an American blend cigarette, as is expanded tobacco, which is puffed or expanded, so the same weight of tobacco holds a larger volume; and also reconstituted leaf, which is a process similar to that used to make paper, to use many of the tobacco by-products to turn them into usable components of a finished cigarette.

Switching to smokeless tobacco, American smokeless products are primarily produced from fire-cured and/or sun- or air-cured tobacco. Flue-cured tobacco is typically not used. They use dark tobaccos, and those are so named because they have a high chlorophyll content. And the smoke from hardwood fires, usually hickory, is generally used in the fire-curing process, which is much like hickory smoke is used to impact that very desirable characteristic to good Carolina barbecue.

Tobacco varieties are varied. I said that at the introduction. There are a large number of cultivars available, both -- well, certainly in commercial production. They're often produced for a variety of different reasons. There are plant-breeding programs at the major agronomic universities -- North Carolina State, University of Kentucky, and others around the world -- that are designed to address resistance to diseases and also perhaps impart additional resistance to tobacco pests.

An interesting factoid I found as well was that the USDA, back in the late '90s, over 1500 germplasms had been archived, as samples there. But the important point is there are at least 60 different varieties of each of flue-cured, burley, and Oriental, that are in commercial production.

There are over 120 countries in the world that grow tobacco commercially. We and other tobacco industry manufacturers source our tobaccos, certainly, from around the world. And the graphic there on the lower right shows a world map. I realize you can't read the legend, but the more intense the color, the larger the production of tobacco. So the red countries -- for example, the United States, Brazil, China, et cetera -- are the top producers by tonnage of commercial tobacco in the world.

Summarizing this portion of the presentation, a slide on total variability seems important because as we talk about the many parameters that impact tobacco leaf and thus the finished product and thus smoke from that product, particularly, obviously, if it's a combustible product, you can look at variability on many time frames. And these are summarized in an annex to an ISO standard, International Organization for Standardization, produced in their Technical Committee on Tobacco and Tobacco Products.

But it could be measured in short term in terms of days. When looking at production of finished tobacco products in a factory, there are obvious variations around specification targets for weight; filter ventilation, which is putting holes in the filter tip to allow air dilution of the mainstream smoke; blend uniformity, because obviously these bulk tobaccos are blended as they're made into finished cigarettes or finished other smokeless products. And these all vary in terms of on order of days, from one machine to another, sitting side by side in a factory.

There's certainly variability that can -- a different degree of variability can extend over the medium term, and that is months, as we look at different components that are used in a finished product because there's variability in the subcomponents, the papers, the filters, for example, any fleece material that be used on a pouched smokeless product, and there are tobacco blend grades, as one source is used up and another blend grade then is moved into production.

Obviously, the major manufacturers have multiple suppliers of these components, so we have interchangeable parts, if you will. Paper from one company is equivalent to paper of another company in terms of performance, but there are minute, certainly, differences in those that come into play.

Then there's long-term variability as we get more into crop year variations, particularly the impact of weather on crop year, component suppliers move in and out of scope, and certainly intentional product design changes. And I'll point out that at least one manufacturer, PMUSA, has discussed some of this specific constituent variability with the Centers for Disease Control.

Move now to some fundamental considerations. The first and foremost concern that I think should be discussed today in front of this subcommittee is articulating clearly the purpose of defining the list. We saw in the first presentation today the requirements of the Act; they're quite clear. But there are a number of possible purposes of such a list, and I'll articulate a few on a subsequent slide.

But that's first and foremost because without knowing that, you don't know how to measure the data, how to collect the data, how to compare the data, and how to ultimately try to use those data to inform or improve public health.

Establishing the purpose of that list, as I said, is also critically important; if there is measurement and testing required, determining the appropriate analytical methods, testing standards, the ability to compare one product to another, one region to another, one year to another.

Some of those examples of possible purposes for listing harmful constituents are evaluating product changes; for example, that you can compare brand styles, or sub-brands -- is the terminology that's used in the Act; you can compare that within a market at one point in time. You can also compare a single sub-brand across time; how does it change year on year.

But there's also other uses for such a list of harmful and potentially harmful constituents, and one is to inform product research, to understand the relationship better between constituents and health risk. Another possible purpose is to set product standards, and a final possible purpose is consumer communication. That is also articulated in the Act as something the Center must address, how and what type of information may or may not be suitable for communication to consumers.

Obviously, in all of this, particularly around setting product standards, is the possible purpose of informing the evaluation of modified risk tobacco products, which is also something of importance to the committee and also to our industry.

The consideration of the public health benefit from establishing a list and any measurements or actions taken therefrom is something that also should be given very urgent consideration because both the agency and industry will likely expend a great deal of effort in dealing with, certainly, provisions of the Act, and perhaps measurement and testing and reporting. And ideally, there would be some assurance that that had some meaningful or measurable public health impact.

But how will that impact be verified, and how will that information be used to advance the public health? And a question that I would articulate for you, which was also articulated in front of the committee this morning in the clarifying questions, was an obvious one. How have the previous reports that have been provided to various public health agencies around the world for more than a decade, how have they been used to advance the public health?

I'd like move to the next section of the presentation, which is really around the scientific framework for selecting harmful and potentially harmful constituents.

It is widely accepted that cigarette smoking causes lung cancer, heart disease, and other serious diseases in smokers. As I've shown you some of the background information -- I'll show you some numbers in a moment -- tobacco and smoke contain many chemical constituents. A number was offered this morning. I will verify that number from the actual citation in just a moment.

Some of these chemicals have been identified as toxic based on laboratory non-clinical tests and perhaps occupational exposure history as well. But also, many of these chemicals are not unique to tobacco. Certainly there are some that are more unique, but there are others that are formed on combustion of any organic material, or the incomplete combustion of any organic material.

An important point in the next-to-last bullet is even knowing all of that, and even after more than 50 years of intensive research, there is inadequate evidence around which specific constituents in cigarette smoke may cause specific smoking-related disease.

While many components can be identified as toxic on their own or in some battery of tests at some concentration, et cetera, if the risk assessment tools that are used are an attempt to sum up the risk of the chemicals constituents in smoke based on their concentration, it only accounts for a few percentage points of the total observable risk.

So it's not known with certainty what constituents are driving which disease outcomes. There's also inadequate evidence that selective reduction of any constituent will actually reduce risk.

We've talked before about the complexity of tobacco. I don't want to over-elaborate that point, but it is something that will play into the discussions today and going forward with this committee. We've talked about the generic and agricultural variables. The smoke from that tobacco is complex due to that inherent variability, plus the other processing and structural components, as I've alluded to.

The reference that was offered this morning, in clarifying a question, there is a recent reference, about a year old, by Drs. Rodgman and Perfetti that gives the most up-to-date list that I'm aware of around the individual chemical constituents of tobacco and smoke, and as was correctly said this morning, 8,000 or more identified constituents in tobacco, and more than 7,000 in smoke.

But the question is, though, how do you take this complex and vast information on chemical complexity and reduce it to a scientifically sound list of harmful and potentially harmful constituents? And the way that I would propose to do that is through, obviously, a scientific framework that couples biology with chemistry. And this leads us to sort of quantitative methods in risk assessment, which again were alluded to in some of the discussion this morning.

But you have to blend what's known about the biology, that is, the hazard, the dose/response, what the toxic effects of the chemicals may be and how much of a chemical does it take; you have to couple that with the exposure, which is really a chemical assessment, to evaluate how users are exposed; are they exposed to enough of the chemical for an adequate duration to cause a toxic effect? And you have to blend those through some sort of a process that is often termed risk assessment or quantitative risk assessment. And only then, I think, can you use that to properly inform risk management.

Just some historical approaches that are based on this concept of risk-based approach. And these were also elaborated in the earlier presentation today.

There are a couple of regulatory advocacy reports that apply, risk-based approaches to the New Zealand carcinogen list of 2000 and the relatively recent WHO TobReg Series 951 report in 2008. There are other scientific publications that also take an approach that we would consider a risk-based approach. I've given you some citations there that span the last decade-plus.

In general, there's qualitative agreement between these lists, and I think that point was elucidated this morning as well. Generally, the same types of compounds and the same numbers of compounds end up on these various lists because nearly all use a modification of a exposure-times-potency concept. And, more importantly, they all use similar assumptions. And that's both a strength and a weakness, I think, of certainly the commonality of assumptions.

So now let's turn to some of the elements for consideration in a risk-based approach, and first is hazard identification. And these are questions posed without answers, at least at this point, but the consideration needs to be in terms of hazard identification. Is it a carcinogen? Does it cause cancer? If so, what type? What is the route of exposure?

Does the constituent have the same hazard as the tobacco product? And this is perhaps a weakness in some of the logic that has been used historically. There's also, certainly, an examination of chemicals in isolation versus chemicals in a complex mixture. And very often, in laboratory settings, those results do not agree.

But to my previous point of having the same hazard as the tobacco product -- for example, benzene is on many of these lists. Benzene causes leukemia, but smoking is not an established cause of leukemia.

Another question to ponder is how robust is the hazard data; what is the degree of uncertainty. There are certainly a variety of types of scientific study that can inform hazard identification. There are laboratory studies. There are animal studies. The are also human studies that can be performed. And also, looking at standard practices about causation, what is the consistency of findings and the weight of evidence.

The second element for consideration in a risk-based approach is exposure. And the strength of evidence that consumers actually receive a biologically meaningful amount of a given constituent is important. For example, is it necessary just to know that it's found in tobacco product or smoke? I would argue that the ability to measure it does not make it toxicologically relevant.

You can also then look at just constituent yield, but you can move further to actually human yield under conditions of use in perhaps non-laboratory settings. You can clearly go to human exposure data in terms of biomarkers. But with each of these, you get strengths and weaknesses, and I'll point out some of those as we go forward.

But just finding it in the tobacco product or smoke has advantages of studying the product. And as you move further down that continuum, you start studying more of the usage behavior. And there's advantages and disadvantages to both, which I'll point out.

Another issue to consider in the criteria for exposure is that some constituents in tobacco and smoke are unique, but many are not. So there are certainly other sources of exposure, which brings in confounding and certainly the relevance of the tobacco smoke exposure for that particular chemical.

So where this leads us to as a conclusion for this section is a quantitative risk assessment, which again has been alluded to this morning. It is an established approach. It's used in the regulation of chemicals in other consumer products in the food industry and certainly in environmental matrices.

It incorporates that necessary requirement of biological potency and exposure in a unified approach that can include both cancer and non-cancer endpoints. It provides a framework for quantitative analysis of uncertainty, which is important, and also the variability inherent in the process required to establish that list of constituents.

It's also flexible. Methods can be scaled to estimate absolute risk or to compare relative risk between constituents, and it can easily be updated as the science evolves. But as with all modeling approaches, it's only as valuable as the input data allow.

I would point out there is some excellent research going on now among a number of industry and non-industry scientists to improve the elements of quantitative risk assessment.

So now, where do we go beyond establishing a list of harmful or potentially harmful constituents? It's a simple fact that there are no standardized methods for measuring most of the constituents being considered. Method standardization, in my view, in our view, has to be completed prior to generation of vast amounts of constituent data; otherwise, you're generating vast quantities of data, but very little information.

The development of any new product-testing regime should be set according to internationally recognized best practice. The International Organization for Standardization is one such organization that has spent decades in a variety of endeavors and fields of interest applying recognized standards. There are other sources as well that can be employed there also.

However, having the standardization in harmonization with the data will ensure that accepted tolerance values exist around which to compare test results. Otherwise, the point that I made earlier about the ability to compare sub-brands within a market, to compare a sub-brand across years, becomes extremely compromised.

In fact, there are many examples of this, where conclusions are made based on apparent variability of a product that are clearly within the tolerance of the analytical measurement error. And those, I would argue, are false conclusions, and those needs to be -- the possibility for deriving false conclusions needs to be addressed. This is one way of doing that, and the best way of doing that. And again, a clear understanding of the purpose for the list is absolutely essential.

When considering testing methods, it's important to focus on some basic methodological considerations. And these are -- for the non-measurement scientist, perhaps, this is basically talking about the ability to measure constituents in tobacco or to generate and measure constituents in smoke. And one of those clearly is the stability over time. You want, certainly, the ability of one lab to repeat the measure and get essentially the same result time and time again.

For many of the components on some of these proposed lists, that's simply not the case. We have seen highly qualified laboratories that, on measuring the same product year to year, get 50 to 100 percent variability. So that is something that has to be addressed, again depending on how the data will be used. And certainly for lower level constituents, that variability with time is quite higher, and it often exceeds the actual range of the measurement itself.

The sampling needs need to be addressed. This is depending on how data are to be collected, perhaps, and reported, how market surveillance may be done. And these are addressed in some of the ISO documents that we referred to earlier.

But, certainly, I think most people would recognize that a single pack of cigarettes is hardly representative of an entire long production run of a particular sub-brand across many months. Maybe not even a carton. Maybe not even a carton in three stores. These are the kinds of considerations that must be taken -- well, given consideration before someone may take an analytical result on a single pack of cigarettes and make inference about how that brand may have moved with time or compared to its competition.

Briefly talk about extraction techniques and smoking methods. Extraction techniques, I'm really talking about tobacco itself, or perhaps also in smokeless tobacco products. There's a variety of ways it could be approached. There could be the attempt to remove everything; I want to analyze every atom in this ground-up sample. Or do you want to try to represent or estimate human exposure? These are important considerations.

In smoking methods, it's very similar. Do you want to try to estimate eh maximum possible yield under any conditions? Do you want to establish a range of likely yields? Or do you want to try to focus in on average human yield? And again, quality standards, ISO 17025, or good laboratory practices should be in place. And obviously, they should reflect the intended use of the measurement.

Move now to some other testing considerations, and we'll talk about these in the order that I mentioned them on the prior slide. And we'll look at, first of all, the laboratory yield, then I'll move to yield in use, and then I'll move to biomarkers.

But looking at laboratory yield -- which is basically you've got a sample in your hands in a laboratory, and you basically grind it up or smoke it without any interaction with an end consumer use. The advantage of that approach is it is the most reproducible. It does permit comparisons over time. You can measure many different chemicals because you have the luxury of having a perhaps potentially unlimited amount of sample available. If you need a higher amount of sample for an analytical method, you simply grind up more tobacco.

Certainly, in the smoke world, there are data from multiple machine regimens. These machine regimens are used to generate the smoke that's collected, then, for subsequent analysis. And there are a variety of those methodologies available. I'll talk about some of those in a little bit more detail, the Cambridge Filter Method, the ISO method, Massachusetts method, and Health Canada.

Moving to smokeless, there's more limited data, but certainly there are data available from extraction of finished products that are available. There's been reporting for years in the United States to CDC on nicotine and pH in smokeless products.

There are a variety of in-house methods that are used in many of the manufacturer laboratories for other constituents, many of which there's a list. Gothiatek, which is a Swedish match internal quality standard that many companies at least look to for some internal guidance for quality purposes.

However, with the laboratory yield measurement scheme, it's difficult to mimic a range of human use. In the smoking regime world, there's no proposal to date that accurately predicts constituent yield under actual human use conditions. And the inter-individual variability in behavior is a key limitation when using laboratory yield data in risk characterization.

We'll move forward to a next middle ground, I would say, in terms of looking at laboratory yield. I mentioned that just having laboratory yield was a key limitation. The more advanced methods of quantitative risk assessment actually try to take into account this inter-individual variability in consumer use behavior. So they're beginning to collect estimates of actual human use conditions.

However, when you do at that time, now you're studying less about -- well, less about the product and more about the actual consumer use, so the variability increases. It is less reproducible.

The data set is currently somewhat limited, but is growing. There are a fair number of studies and data points available, as you can see in my footnote, for yield in use, which is filter testing for actually human-smoked cigarettes. But it can also be applied to smokeless, where you analyze the sample product before and after use and then look at the actual yield of constituents based on a difference measurement.

When you apply it in a probabilistic risk assessment, you can actually partially account for inter-individual variability and behavior. And that we think is an advantage to using some of the more recent quantitative risk assessment tools.

There are certainly some scientists who might advocate for testing biomarkers of exposure in constituent regulation. However, there are a limited number of biomarkers available. They certainly can provide an estimate of biological dose, but there is uncertainty about the disease relationship to many biomarkers, certainly, of exposure. There's a lot of interest and activity in trying to identify biomarkers of harm, but I don't think we're necessarily there yet.

Again, as you move further down the continuum away from the product and more toward the end user, you're going to increase variability. And that is certainly true with biomarkers because now it's not only the constituent that's yielded from the product, it's how much is inhaled, how much is absorbed, how much is metabolized, how much is excreted. All of these steps add variability.

Some testing considerations. Certainly there are members of the regulated industry that have a great deal of relevant experience in this area and are certainly willing to provide additional detailed presentations on any of these topics to this committee or to other interested parties, as you may see fit, whether it's the possible development of laboratory methods, looking at what I would call the human use or the yield in use studies, or whether they're biomarker studies, or even the knowledge that's been gained over the alternative smoking regime situation over the last 10 or 15 years.

Oh, sorry. In this last section of my presentation, I'd like to focus on some potential technical objectives of smoke testing methods and offer an historical perspective. Certainly some potential objectives of developing methods for smoke constituent measurement could be developing an understanding of, certainly, the intended purpose of a regime, the scope of human smoking behavior studies, relevant uptake studies, possibly the scope of alternative smoking machine regimens, and also looking at the repeatability and reproducibility characteristics of any of these alternative smoking methods.

For an historical perspective, I'd like to focus on the relevance of machine yields to smoke yields experienced by smokers. Both government and nongovernment bodies have for some years now rejected the idea that machine test yields, based upon a single smoking regimen, equate to what an average consumer obtains from smoking, which raises an interesting question, and that's the historical perspective, technical capability versus promulgated regulation. And the question that one should ask is which should come first.

This chart lists an example of some historical and current machine-based smoking regimens that include the FTC method, or the method formerly known as FTC, which was used in the United States historically with a stated purpose of cigarette yield ratings for product comparisons.

The ISO method, International Organization for Standardization method, is an international standard used in many countries for the same purpose, same stated purpose, cigarette yield ratings for product comparison.

More recently, the state of Massachusetts, for example, has implemented regulation, the stated purpose being to estimate nicotine yield for an average consumer. And then in the Canadian Intense regime, which is applicable in Canada, the stated purpose is to estimate the maximum yield under realistic conditions. And the emphasis there on "average," "maximum," and "realistic" is mine because I'm going to return to those topics in just a moment.

So let's look at the FTC method, which dates back to the '60s that remind you of the stated purpose, cigarette yield ratings for product comparison. It is an example, in my view, of technical capability preceding regulatory testing requirements because the inter-laboratory harmonization was conducted in 1964, before the method was put into use.

Therefore, when it was applied, the variability was understood. Within a laboratory, between a laboratory, there were tolerances established so a scientist and a regulator would know how to interpret differences in test measurements, and those numbers are summarized here.

Basically, the variability in the methods determined that the reporting precision for tar was to the whole milligram. There's no reason to focus on fractions of a milligram because the method doesn't allow you to do that. And for nicotine, it was a tenth of a milligram. So the method was suitable for that stated purpose, cigarette yield ratings for product comparison.

We move to the Massachusetts method in the late '90s. The stated purpose was to estimate nicotine yield for an average consumer. Again, that's my emphasis. I think this is an example of regulatory testing requirements that actually preceded the technical capability. There was no inter-laboratory harmonization conducted prior to the regulatory implementation. Therefore, the method variability was unknown within a laboratory, and certainly among or between laboratories.

But an assumption was made that reports should be based on the FTC method accuracy, which was to a tenth of a milligram of nicotine. And for those of you that know the essence of these methods, I mean, this is a more intensive smoking regime. It generates a larger amount of smoke. Therefore, it has a higher inherent absolute variability. So the method variability is clearly higher than was assumed based on the previous FTC results.

So what's the relevance of the Massachusetts machine yield to its intended purpose? And I state again there what the intended purpose was stated to be. I don't show you the data here, but I certainly would be happy to show data if it were appropriate.

Based on yield and use data, which is actual human yield data compared to machine yields, the nicotine yields under the Massachusetts regimen do not indicate what an average consumer will inhale into their lungs, therefore, when they smoke a particular brand of cigarettes. So I think it leads to a reasonable argument that this method does not fulfill its stated purpose.

Finally, move to the Canadian Intense example, which I would argue is another example of regulatory testing requirements that are preceding the technical capability. Remind you again of the stated purpose, estimating maximum yields under realistic conditions, again, my emphasis.

As the case for the Massachusetts method, there was no inter-laboratory harmonization conducted prior to the implementation. The method variability is unknown between and within laboratories. So then we look at the relevance of that to its stated or intended purpose. And I think it's fair to say that the Canadian Intense smoking regime, which is a reasonable approximation of the maximum mouth level exposure -- or, sorry, the mouth -- yes, right, the mouth level exposure that could be yielded from a cigarette.

I know certainly all of the people around the subcommittee table are familiar with this. But for others, the Canadian Intense method employs wrapping the filter with cellophane tape to prevent any infusion of air to dilute the smoke. It blocks completely the filter ventilation. So while it does afford a reasonable approximation of a maximum mouth-level exposure, it leaves the second issue of stated purpose as to how realistic is it. So we ask that question.

A couple of assumptions here. First of all, this procedure of taping the filter and blocking the vent holes, it assumes that smokers fully compensate for nicotine when switching from high- to low-yield cigarettes. There are many studies that show that compensation is not complete, and also that many smokers of highly ventilated cigarettes are not switchers. They don't switch from higher-tar to lower-tar products. It's always been their usual brand.

The relative composition of smoke is only meaningful if it's similar between machine smoking and human smoking conditions. And in this case about ventilated cigarettes, it's unlikely to be true because smokers do not block all vent holes, and there's sufficient research on that to show that while some vent blocking occurs, it is not as widespread as was believed ten years ago.

Also, there's certainly the possibility and there's certainly emerging evidence that the unrealistic changes occurred during tobacco combustion because when you tape the vent holes, draw an extreme volume puff, you change the burning characteristics, the peak temperatures during a puff, the filtration efficiencies of the cigarette filter. Many of these things are changing in ways that may seem small but may have unintended consequences.

So I would argue that the lesson that should have been learned from these historical examples is that technical capability should precede promulgation of new regulation.

So finally, I'll conclude by restating the takeaways. I think identifying a clear purpose for the list is critical, both to inform the Center, to inform public health, and to inform the industry. Remind you that tobacco is an agricultural product with substantial variability from sources, some of which can be controlled more than others. And the framework for developing a list of harmful and potentially harmful constituents does need to be science-based. I think we all certainly agree to that in principle. And obviously, any testing or reporting of constituents must be based on properly standardized methods that are validated and fit for purpose.

With that, I thank you for your attention.

DR. HATSUKAMI: Thank you, Dr. Ogden.

Questions at this point in time?

Yes, Dr. Farone?

DR. FARONE: Yes. If one looks at measurements of any individual constituent, is there any opinion among the industry as to what represents an acceptable -- I'm thinking of your quantitative risk assessment -- an acceptable risk from use of any of the products?

DR. OGDEN: Well, first of all, a disclaimer. I'm not a toxicologist. I'm not a risk assessor. And we have scientists that could answer your question more intelligently than I can. There are certainly ways to prioritize and to make calculations of risk. And, obviously, any numerical number can be rank ordered.

As to the specific answer to your question about acceptable risk, I believe there are some considerations that are generally used across -- in toxicologic and risk assessment circles. I've heard numbers, you know, one in a million. But I'm not an expert there, so I couldn't answer that question.

Obviously, for all of these questions, I'll look to the other members of the represented parties.

If they want to wave their hand at me, I think, if it's acceptable to the chair, we can identify and ask them to comment as well.

DR. HATSUKAMI: Dr. Henningfield? You have a question?

DR. HENNINGFIELD: I wonder if you could go back to slide number 22 because I might have misunderstood.

DR. OGDEN: Wait a minute. I probably shouldn't have done that. Twenty-two, enter. Oh, that was too easy.

DR. HENNINGFIELD: Thank you. The second, "There is inadequate evidence that specific constituents in cigarette smoke cause any specific smoking-related disease in cigarette smokers," it seems like a remarkable statement. There are a number of constituents, I couldn't acetaldehyde, carbon monoxide -- what am I missing here? And in particular, nicotine -- I assume you're not going to say that nicotine does not cause nicotine dependence and withdrawal.

DR. OGDEN: No. I wouldn't say that.

DR. HENNINGFIELD: Then that statement -- then what am I missing? That statement doesn't make sense to me.

DR. OGDEN: Let me try it again. This was in reference to the first bullet, where we were talking about the smoking-related diseases of lung cancer, heart disease, et cetera.

The inadequate evidence that I'm referring to here is that while many of the individual constituents have been related to some disease endpoints, there is not a specific relationship in the context of cigarette smoke. In other words, we don't know what constituents cause a particular disease.

For example, nitrosamines, tobacco-specific nitrosamines, are lung carcinogens. They are in tobacco smoke. Tobacco smoke is a cause of lung cancer. But there are also levels in smokeless tobacco products that does not cause lung cancer.

So there's a great deal of uncertainty in trying to attribute which constituents in the smoke matrix are driving an independent disease outcome, for example, such as lung cancer. The nicotine dependence question is an obvious one because, by default, it's nicotine. But these are the more complex disease states. It's not known with certainty which chemicals or which combination of chemicals or what threshold would be to cause a disease.

DR. HATSUKAMI: Yes. Dr. Burns?

DR. BURNS: That was an interesting presentation, Dr. Ogden, and I had a couple of things that I wanted to follow up on.

You mentioned that you source tobacco from multiple different countries and locations, and obviously different agricultural practices, et cetera, although I assume that you specify some of that in purchasing the tobacco. Do you measure in the tobacco that you source constituents of that tobacco, specifically benzpyrene, nitrosamines, and heavy metals, from those different sources?

DR. OGDEN: Certainly not in every bale of tobacco that would be purchased. I mean, we do -- there are research studies that go on that have relationships between some of those constituents, and in particular, of the agronomic variables, growing regions, soil conditions, particularly for metals, and those kinds of things.

So there's information there, but on an incoming lot of tobacco, I'm not aware that we do that, and I'm not aware that that's a common practice. No, sir.

DR. BURNS: Well, the issue would be getting some handle on that variability for purposes of our deliberations. And it would seem that if you're sourcing materials that have substantially different levels of identified toxicants in them, that you might have some handle on what you're actually receiving.

That sort of goes to a second question I have, which is --

DR. HATSUKAMI: Yes, go ahead.

DR. LEWIS: Yes. I'm Dr. Jane Lewis, and I'm here on behalf of Altria Client Services, representing Philip Morris USA and U.S. Smokeless Tobacco.

Just in response, Dr. Burns, to your question, I think our emphasis has been more on measuring some of these constituents in final products as opposed to incoming materials. If you do look at constituents in incoming materials, you can get an understanding of the variation, as you suggest. I think what you'll also find is that that's not consistent.

You may measure a lot of tobacco from one part of the world one year, and the next year the climate conditions may be different. It may vary from region to region. We have drought years. We have flood years.

So what you'll see overall is a pretty high-level variability. And I'm not sure that you'll get a real consistent picture, really, over the course of time by doing that. So we focus a lot at Philip Morris USA, for example, and U.S. Smokeless Tobacco Company, when the products come in. We try to control the products as they come in not to increase those constituent levels. But we're pretty much at the mercy of the agronomic conditions and the weather conditions of what comes in the door.

DR. BURNS: Well, but one would assume that if you're concerned about the outcome levels, one would want to know something about what's happening in terms of the product you're purchasing.

But it goes to the second question that I wanted to ask Dr. Ogden, which is, as a scientist, not speaking as a formal position for the company -- I realize that that's not appropriate. But as a scientist, would you agree that if you have identified human carcinogens present in a product, that you would have an obligation to reduce the levels of those carcinogens to the lowest levels that are technically independent of a clear demonstration that that reduction by itself would alter disease outcomes? Just speaking as scientist.

DR. OGDEN: Sure.

DR. BURNS: I'm not asking you to express an opinion for the companies.

DR. OGDEN: Well, and if I were doing that, I would clarify that difference.

I think the notion that you speak of is a principle that many people would endorse. And philosophically, I would agree with that. But there are certainly -- there are other bits of information that are incredibly relevant to that discussion as well.

First of all would be what is the relationship of that particular constituent to the disease outcome in the product as it's used. While it may be related in some laboratory animal studies, if it's not relevant in terms of route of exposure or in terms of the amount of material presented, it may not be worth the resources to try to reduce that.

But if you could, and not dissuade any other more advantageous activities that might impact public health, I think you would do that. We have done that. Looking at the indirect curing of flue-cured tobacco, we can reduce nitrosamine levels in flue-cured tobacco, and we did that, on the premise that you've stated. Lowering it, it didn't change the taste of the tobacco, it didn't put farmers out of business, and it's the right thing to do at that level.

We then conducted every chemical and biologic test that we knew of to see if that actually reduced the risk, and it did not. So we do that, but if doing what you suggest takes resources away from things that may be more related to a net positive public health outcome, I would argue that resources would be better expended in other places.

DR. BURNS: Well, the question is really driven at the response that you made, which is, is there an obligation, with defined, clear, unequivocal human carcinogens, for the companies to produce the lowest level of those constituents, independent of being able to establish that that reduction in that carcinogen will have a clear and defined provable reduction in disease risk?

Most products, if you have carcinogens present, the companies are obligated to remove those carcinogens to the extent that it's achievable in the manufacturing process. And the question is why the tobacco companies would be exempted from that kind of philosophical approach and be entitled to say that they don't have to reduce carcinogens until it can be proven that the level of reduction would alter a specific disease occurrence.

DR. OGDEN: Well, if the intention of this list or removal or reduction is to inform public health, I think that's the standard that we would apply. If there's no intention of informing public health, if it's just the right thing to do based on some precautionary approach, then I think it's tempered by other elements of reality.

When you say "to the lowest extent possible," that raises a number of questions. What is the extent possible? What is the extent possible without driving certain farmers or countries out of the business of growing tobacco for commerce? What is the ability, the supply of the tobacco, to all of the manufacturers around the world?

There certainly will be other impacts that have to be assessed before you can say, reduce it at any cost to any level.

DR. LEWIS: Dr. Hatsukami, may I respond as well?

DR. HATSUKAMI: You can add.

DR. LEWIS: May I respond as well?

DR. HATSUKAMI: Sure. Yes.

DR. LEWIS: Dr. Burns, I think a way to look at this is that when those carcinogens are removed from other products, the point is to make those products safer.

I think, from what we know about cigarette smoke and tobacco, you could remove these constituents and it's not known whether you've made those products safer or not. And that would be the goal of trying to do that.

At Philip Morris USA, we also have experience trying to selectively remove many of these constituents. We measure the results of that work using a variety of tests, smoke constituent analyses, biological analyses, biomarkers of exposure, and some biomarkers of potential harm. And it's difficult to see that link to disease, that you've actually made a product that potentially could be safer.

So I think, really, it's going to be up to this committee and the agency to make that decision whether we should focus on this or not. I think the point where we would come from at Philip Morris is that the disease risk in humans and the population harm is important, and to focus on things that are known to affect that disease risk and that harm, and that would be things like the smoke exposure in total, and go back to the continuum of risk. That was something we presented in our submission to the agency back at the end of the year.

Clearly, stopping smoking is important in reducing harm in the population. Reducing the number of years smoked, reducing the number of cigarettes smoked per day, and reducing smoke exposure for people who continue to smoke, reducing that total smoke exposure by alternative products such as smokeless tobacco products, is another proven way of reducing smoking-related diseases.

So I think the point here is, what is the purpose of doing constituents work and constituents testing? We've used lists for a number of different reasons, but kind of what is the purpose of doing that?

DR. BURNS: Well, I would strongly disagree with you that other products who have limited or removed carcinogens do so only to the extent that they can prove a difference in the type of testing that you're doing on cigarettes, that is, mutagenicity and other types of testing. They do so based on the characteristics of the product, that is, its toxicity and the fact that it is possible to lower it rather than being obligated only to lower it if they can prove that there is a reduction in biologic toxicity.

DR. LEWIS: I'm sorry. We're speaking in general, and I was thinking of something like food, perhaps, which is typically assumed to be a safe product and you would want to ensure that it's safe. So we may be talking about different types of products.

DR. HATSUKAMI: I think we'll move on.

Dr. Henningfield, did you have a question?

DR. HENNINGFIELD: I have a comment. But following up, there are products like the drinking water that we have where I think this principle applies, where there are maximal standards for allowable chemicals, et cetera, including from the packaging, from the plastic material, that are not set on the basis of whether one bottle of water is safer than another bottle of water. And the same thing with foods.

But talking about foods, you opened up with quite a bit of discussion about the inherent variability of tobacco as an agricultural product. And I guess, from the perspective of regulating and setting upper limits on some constituents, I don't see that as a problem. We already accept that with foods, where whether it's pesticide residues or heavy metals, upper limits can be set. Dr. Burns mentioned a couple of other examples. You mentioned things that you test per bale.

So it seems like if we were talking about regulation that asked the industry to precisely hit a target of what a toxicant level should be, that's one scenario.

Another scenario is regulation that sets upper limits, performance standards, how much heavy metals, how much aflatoxin, how much whatever, pesticide residues.

How is the fact that tobacco products include an agricultural product, how does that complicate that? I don't see it.

DR. OGDEN: Well, one of the elements of an answer to your question is in relation to food, I think there is a disconnect because food, everyone would recognize, is intended to be safe. We know that tobacco products have inherent risk, whether it's smoke or smokeless, and they have a different degree of risk.

So I don't know to what extent the applicability of performance standards in food may be applicable to tobacco. They may. There certainly could be some overlap there. There certainly could be some guidance there because, obviously, they are agricultural products.

I don't know, can't speak with authority, to what extent tobacco is more variable and from more sources around the world than commercial corn, for example. I suspect that it is, but I may be wrong. So I don't know. But there certainly could be some parallels to the food regulation of raw materials, and I think that would be worthy of consideration.

DR. HENNINGFIELD: But to follow up, the Altria -- I'm sorry, I don't recall your name -- the Altria representative --

DR. OGDEN: Dr. Lewis.

DR. HENNINGFIELD: -- Dr. Lewis, gave a number of examples which make the point that the risk and harm caused by tobacco is very much a function of how it is made, what's in it, what the product is, how it is used, smokeless tobacco being an extreme case, and the list of manufacturers that is included in your disclosure at the beginning includes, including your own company, companies that have already made claims about reductions in levels of certain constituents and the relation to disease.

So it seems like a big disconnect from that to now be saying that we don't know anything -- I'm paraphrasing, but to go back to that slide number 22, that there's inadequate evidence about anything specific, it seems like a big disconnect between what I've heard already this morning.

DR. OGDEN: Well, let me give this -- well, first of all, I'm not sure I understand your -- it seemed like you suggested that some of the Reynolds companies may have made a statement -- and I forget the way you said it, but I'm not aware that that's the case. But a specific example here, I think, may help.

If we could reduce tobacco-specific nitrosamines in tobacco smoke, would there be a measurable reduction in lung cancer attributable to tobacco smoke, tobacco smoking? I think the answer is, we don't know that.

We could also go about an activity of trying to reduce tobacco-specific nitrosamines in smokeless tobacco. And the question now becomes very interesting because not only could you not -- you can't measure a reduction in lung cancer rates in smokeless tobacco because it's not associated with lung cancer anyway.

So it's not the chemical. You have to take into consideration other factors, the complexity of the mixture, the route of exposure. And to the extent that a scientific standard could be upheld, that that is meaningful, that that is useful -- and this committee is tasked with doing that; I'm just offering some guidance. But to the extent you can do that, then, yes, it's a worthwhile exercise to try to accomplish that.

Our suggestion here is that, basically, the resources expended around any of these potential topics should be proportionate to the risk. The more you know about a particular constituent being attributable to a smoking-related disease, for example, the better able you are to perhaps influence that with growing practices and technology. That would be a higher priority than things that -- constituents that may not have the ability to be reduced, or may not be linked with the smoking-related disease.

DR. HENNINGFIELD: Just one follow-up. Oftentimes you advance, I think, in science and regulation on proof of concept, proof of principle, and examples. Sometimes they're not necessarily practical. But again, if we look at the list of companies that have contributed to your presentation, they've marketed products, made claims, and presented some data that a lot of us have written about and thought there was some demonstration of principle.

That includes RJR's Premier, Eclipse. Philip Morris Accord. Santa Fe products. The different smokeless tobacco products. Some of the different products that U.S. Smokeless is presently marketing now with -- I think I could come up with several other examples.

But the companies have already talked about reductions in specific constituents in relation to biomarkers and to disease endpoints. So again, you've already done it.

DR. OGDEN: Well, but you've left out the whole middle ground. That's not a relationship, at least for the products that I'm aware of in the Reynolds portfolio. That's not a single constituent measure. I'm not aware of anything, certainly in recent history, or at least with my experience with the company, where we have said reduction of a constituent equates to reduced risk.

If you look the Premier example, which you gave, there's a 500-page book that outlines not only chemical constituent testing, but it outlines in vitro testing, comprehensive in vivo testing over multi years, multiple rounds of exposure. It looks at human exposure. So it's a comprehensive package of information that would be used to make that kind of a statement, from my perspective.

If you go to smokeless, you can certainly rely on epidemiology around the world that demonstrates certain types of smokeless are far less riskier, in my opinion, than combusted tobacco. So that's not based on constituent information alone. It's based on all a battery of toxicologic tests that we and others have tried and worked hard to establish over 20 or 30 years that give us more information there.

DR. HENNINGFIELD: That 500-plus page Premier monograph has a lot of specific constituents in the testing and product design that I think there are some actual parallels in what we're trying to do here.

DR. OGDEN: Well, let me finish that up. That is a natural progression, in my view, of looking at exposure versus potency, which was the summary of some of the slides that I gave here. We do chemical constituent testing. We have for more than 50 years. We don't stop there.

So you look at the chemistry. You look at the in vitro biology. You look at the in vivo biology. You look at the human data, to the extent it's relevant. And only when you get that package of data, in my view, can you make an assessment like you've just suggested. That's not based on chemistry.

DR. HATSUKAMI: Dr. Lewis, if you want to make clarifying points, and then Dr. Farone.

DR. LEWIS: Yes. We have studied products as well -- you mentioned the Accord product -- and we've published quite a bit of that information. And we did study individual constituents and reductions. We did study results in biological tests. We looked at biomarkers of exposure and biomarkers of potential harm and clinical studies, and we've published that.

But we've not made any consumer claims around that information. That is one of the reasons that Altria has supported the passage of the statute, was to help lay a framework within which a modified risk product could be manufactured, and test data could be generated, and potentially a claim could be made. Because we couldn't see a clear enough link between those measures and disease risk to be able to make a consumer claim.

We also have experience with a selective reduction program where we put carbon in the filter. We marketed that product as an Ultra Light product. Made no specific claims about that product, either. And did all those relevant measures on that product, but again, we didn't find a connection between the reductions in constituents that we found, as measured by biomarkers of exposure.

In that case, with the carbon-filtered product, we did see reductions in biomarkers of exposure. But the biomarkers of potential harm that we measured, which you could argue may or may not have been the relevant or the right biomarkers of potential harm, didn't change. If anything, in a statistically nonsignificant way, they might have gone in the direction of increased harm. So we didn't make any kind of consumer claim about that product, either.

DR. HENNINGFIELD: This is the Marlboro Ultra Smooth program?

DR. LEWIS: Yes. I may have said that

wrong. Marlboro Ultra Smooth was --

DR. HENNINGFIELD: I'm not sure if you mentioned it. I wanted to make sure.

DR. LEWIS: Yes. It was the Marlboro Ultra Smooth. That's right.

DR. HENNINGFIELD: The data that you have from that, and I understand you had extensive biological data in the sampling in your studies, is that data that are already available or data that could be obtained?

DR. LEWIS: Upon request from the agency, we could provide that information. A lot of that information has been published.

DR. HATSUKAMI: Dr. Farone?

DR. FARONE: I'd like to use a specific example, Dr. Ogden, without you needing to agree that it's valid.

But let us suppose that 14 nanograms per day of NNK provides a risk of 1 in 100,000. And let's say that there's a scientific body of evidence that validates that particular number. Is it then not reasonable, or would it not be -- I'm trying to get a clarifying idea here about what we're saying with regard to specific constituents. Would it not then be reasonable to try and reduce NNK below exposure rates of 14 nanograms per day?

DR. OGDEN: With the presumption that you would then drive down that mathematical calculation of risk attributable to that.

DR. FARONE: With the presumption that wherever it comes from, it provides that same level of risk.

DR. OGDEN: Well, but we know that it doesn't, and I guess that's one of the scientific disconnects that I have. So the same level of that nitrosamine you mentioned in cigarette products versus smokeless obviously carries a very different risk for lung cancer.

DR. FARONE: Yes. I'm talking about cigarette products for inhalation.

DR. OGDEN: Well, but I don't think you can totally disregard the other because it raises back into focus many of the other points that I made, is the relevance of the chemical in the human disease state, the complexity of the matrix, the route of exposure, and not only the dose.

As a mathematical exercise, I would agree with you. But to the extent that that's not demonstrable in terms of a real reduction of public health risk, the resources may be better spent in another area that could demonstrate reduced risk.

DR. FARONE: But how about as a measure of your quantitative risk modeling that you mentioned as being something that we should be doing?

DR. OGDEN: I'm not sure. Your question is -- I'm sorry. I'm not sure what your question is.

DR. FARONE: Well, if I pick 14 nanograms per day -- we can argue about whether that's correct or not, but let's say we pick that -- and so that's a risk of 1 in 100,000. So now I can look at cigarettes by inhalation of different types, different brands, and try to see what happens, how close the numbers, by different methodologies, by different measurements, comes to that particular value.

DR. OGDEN: Well, again, whether the numbers are right, I don't know. I'm not a risk assessor.

But this brings, I think, into scope one of the other elements that I tried to make the point of.

The example that you're making is what I would call a deterministic approach. You've got a single number, you reduce it, and it drives a single number down. I think when you go into what I suggested as a more reasonable approach to quantitative risk assessment and talk about the probabilistic approach, the input parameters around exposure, around your 14 nanograms per day, is not a single number. It's a wide distribution.

When you employ those approaches and make the calculations, it's not that clean. It's not a one point to one point. It's a distribution to a distribution. And whether or not that's a meaningful reduction, I think, is open to -- to really drive public health impact I think is open to scientific debate.

DR. HATSUKAMI: Any other questions?

[No response.]

DR. HATSUKAMI: Thank you, Dr. Ogden.

We will move on, then.

Our next presenter is Dr. David Johnson from the Council of Independent Tobacco Manufacturers.

DR. JOHNSON: Thank you, Madam Chairman, members of the committee.

Good morning. My name is David Johnson, and I'm representing the Council of Independent Tobacco Manufacturers of America. And I'm going to talk to you today about some of the issues that the small tobacco producers have with regard to the production of a list, and how that needs to be considered as you start to put together any list and start to think about how you would implement those types of activities for the promulgation of regulations that may impact tobacco-related products. Okay?

The first perspective that the small manufacturers have is that this list really should be something that's really guided and based on science. It should be science-based, focused on the harm that can be caused, and should really not be used to try and attempt to put small manufacturers out of business. That's not the goal. The goal is to impact public health in a way that all the producers can produce products that can meet the requirements and then meet the public health need.

Also, this committee's recommendations really should be based on sound, peer-reviewed science that's not focused on anybody's agenda, but focused on what really addresses public health.

The list of components should be explained to the public in an adequate way because any time you produce a list, you're going to have the data be out there somewhere. The consumer's going to see it. There's going to be a perception. The perception is that smaller numbers means that it's a safer product.

That isn't always the case. Smaller numbers mean smaller numbers; it doesn't mean that it correlates to a product that is now safer or produces an impact on public health that's beneficial. So I think it's important that the public be informed in a way that is meaningful so that they can understand what this data can tell them, and the extent to which they can use that information.

The list also should be reasonable based on the fact that the small manufacturers don't make claims about reduced risk or modified harm. What they're doing is making a product that's a generic product for sale.

If you look at the market share reality that exists for small tobacco manufacturers, these manufacturers produce products that comprise approximately 4 percent of the total cigarette marketplace, and that's more than 200 companies that are involved in the production of 4 percent of the total production.

So their resources are very limited. They don't have the resources to do the things that large tobacco does. Large tobacco companies have large research organizations. I used to work for one, and they had a very large research organization. And so the major tobacco producers have organizations that have a long history of being staffed with very highly capable scientists with lots of equipment to do lots of testing.

The small manufacturers, unfortunately, don't have those resources. They don't have scientific staffs. They don't have large batteries of equipment to operate with. And they have to rely on third party laboratory testing in order to be able to generate the data that's going to be required from any list that gets produced. The consequence of that is that the expense and the availability of testing really is going to be one of the things that is going to be important to small tobacco manufacturers.

The large tobacco producers can and have been looking at the Hoffmann analytes for a very long time. And they have the ability to do that testing, and they can do it in-house in most cases. Small companies cannot do that. They have to go outside, and so that capability has to exist. And the methods that are going to be used have to be competent, capable, validated methods that have a scientific basis Dr. Ogden described. And I agree with him. Those are the key criteria for any testing that has to be done.

But the small tobacco producers generally make conventional products. They purchase generic components and tobacco leaf, and they manufacture without a lot of high-tech capability. But they make consistent quality products.

They operate fundamentally without a large number of scientists in order to be able to do this work, and they tend to rely heavily on a lot of the fundamental science that's produced by the large tobacco manufacturers because they have the capability, they have the resources, and they have the knowledge, and they're using the same materials. So that makes sense from their perspective based on the economies of scale that they have available to them.

These small companies have to make sure that the third party testing laboratories that they have for determining product conformance have current available test methods that allow them to meet the requirements that the regulations may set.

The reality is that these producers produce conventional, traditional products. They have huge costs for testing compared to the economies of scale for large tobacco companies. They are limited in their ability to have control points in the processing and selection of leaf because they don't have the connections with the leaf growers to be able to influence the agronomic practices that exist in the production of the leaf, that get done in the curing of the leaf, or in the other points where you can control the level of constituents that exist in tobacco leaf.

In general, these things are products that are grown in the soil. The heavy metals are taken up by the plant, just like any plant that's grown in the soil, and it doesn't matter whether it's a food product or whether it's a tobacco product. Those heavy metals are going to be taken up by the root system, translocated to the plant, are going to lodge in the plant tissue, and so you have that function. That's something that's a function of where the tobacco's grown and the conditions that exist at the time that it is grown. That's something that they have no control over, nor does anyone else, for that matter. But these things are all important as you start to think about what are the constituent levels going to be in the tobacco.

The small tobacco product manufacturers are limited in their ability to stay in business if the cost of analysis becomes excessive, so that the financial burden can be excessive on the small producers.

I want to talk a little bit about what that list of harmful constituents might look like based on the perspective of the small producers. I think this is fairly consistent with all producers, but there needs to be a rational and fundamental scientific review of all of the data that exists to make sure that all of these components are things that are associated with harm, and that they are then something that you can look at and say, we're going to have an impact on health, public health, that we can say that by managing this product and setting these specific thresholds, we can have a product that's going to say, we have the safest tobacco product we can produce.

I caution you to take that word "safest" with some caution because I don't mean to imply that tobacco products are safe. I mean that you are taking a product and making it as safe as you can make it, given the things that you have to work with.

It has to be based on the current capabilities of the industry in order to be able to control, analyze, and/or remove constituents that are considered to be of toxicological significance. And it needs to be technology that's available broadly across the industry because if it's a proprietary technology, you create a monopoly, and that's not necessarily a good practice.

The constituents that are considered should be justified in terms of how the final data is going to be used; what is the purpose of gathering the information, as Dr. Ogden pointed. And I think that's a critical parameter in looking at whether or not this should be included in the potential list of harmful ingredients.

The testing must be reproducible and priced to be accessible to small companies. The testing has to take into account also the global capability to do testing because, as I said, the small companies don't have the ability to do the testing themselves. And if you require testing that exceeds the global capacity to be done, they can never generate the information required in order to meet the regulatory requirement.

Finally, from the perspective of the small tobacco producers, there needs to be a position, in terms of the recommendations that they would make, that we need to have convened a permanent industry advisory panel of scientists to work with the FDA scientists on constituent evaluation and identification, not constituent evaluation in terms of what's in tobacco or what's in tobacco smoke; that work's been done. You've heard several times this morning about a reference that exists that shows that there are over 8,000 compounds in tobacco and over 7,000 compounds in tobacco smoke.

Those are excessive numbers. Not all of them are toxicologically relevant. But there needs to be a discussion at the scientific level of which constituents actually constitute things that cause harm, which constituents are the ones that are the most relevant to be placed on this list, and that can then have the ability to be used to regulate the products in a way that minimizes the heart risk associated with the consumption of those products; that the Federal Data Quality Act standards should apply to the inclusion of any constituent on this list; that the testing should be limited to the top constituents, based on the assessment of the relative risk to human beings. So that's one of the critical elements. The risk should be human-based risk, and it should be really focused on which things really impact that.

Then the small companies, because of the fact that not everything needs to be tested -- some things can be estimated based on testing of a small number of components -- believe that allowing them to test only the primary constituents and then extrapolating and estimating the others is a reasonable approach.

When you think about it chemically, that makes sense. what are we looking at? You're looking at a pyrolysis process. You're taking a product. You're burning it. Science says that if I do this with the same compounds, the same product, that I burn it under the same conditions, the same profile should actually be generated regardless.

So the ratio of the various compound classes shouldn't really functionally change as long as the parameters that I establish are set and defined. But that presumes a lot of things. It presumes that the person who's smoking a cigarette smokes a cigarette the same way every time they smoke one. That's not true.

It presumes that the temperature profile of the pyrolysis stays the same. It doesn't. It presumes that the composition of the tobacco product is fixed, and that's almost true because the tobacco's blended and you try and get to the point where it's as consistent as it can be, given that it's a raw agricultural commodity and these things are inherently variable.

But for the most part, data shows that calculations can be done to estimate the amount of various classes of chemistry based on the measurement of some key constituents. If the primary components of the products produced by the small manufacturers are essentially the same, they would ask that they be able to report them based on substantial equivalence and the benchmark currently established within tolerances for similar products produced by large manufacturers, which once again addresses their ability to meet the requirements without the excessive financial burden that would be imposed under the condition that they had to go out and independently, at a third party, buy those services, which they do not have currently built into their fixed costs.

I think that's all I have at this point, unless you have questions for clarification regarding the position that the small producers of tobacco products would have you have this morning regarding this list.

DR. HATSUKAMI: Questions?

Yes, Dr. Henningfield?

DR. HENNINGFIELD: Just to clarify, when you're talking about standards that should be set for small versus large companies, what I'm not sure I understood is if you mean the problem is how to pay for it, or capacity, or whether there should be standards. And by example, use my drinking water again.

As a consumer, don't you expect that any drinking water not exceed certain standards for bacterial contamination, heavy metals, whatever, whether it's produced by a giant company or a tiny company?

DR. JOHNSON: Well, I may have misspoken or you may have misunderstood what I said. I wasn't saying that there was any desire on the part of small tobacco producers to have no standards or that the standards be different. The way in which they achieve that has to be different because of the economies of scale that they have.

If you say that there's a standard that says we are going to have this level of these five constituents in the product as produced and used, that's a standard that has to be met by everyone. I work as an independent consultant so I can't tell you what they would think. But I'll tell you what I think as a scientist. All right? Is that a fair statement?

As a scientist, I believe that those standards have to be whatever the standard is. But the standard should be based on human risk, that that standard should be set not based on what the analytical capability of any company is because you can measure things that have absolutely no relevance to human health.

In your bottle of water, yes, there should be standards around biological components. There should be standards around pesticide residues. There should be standards around heavy metals. There should be standards around a lot of things because that product is being used, and it has an expectation that it's going to be consumed in large quantities, it's a requirement by everyone, and it's now something that has an expectation of being safe.

Tobacco products are slightly different, not that they shouldn't have standards, not that those standards shouldn't be met, and they should be met by everyone, regardless of the size of the company. But how do you meet that is what the small companies are trying to get at.

They're not saying, we don't want to meet those standards. What we're saying is that the way we have to meet those standards, because of the profitability in that part of the industry, because of the size of those companies, because of the lack of capability to do external testing, because of the physical limitation of that resource, that their needs are such that they may ask that the way in which they accomplish that doesn't have to be the same as, say, a very large tobacco company that has hundreds and hundreds of scientists and many multi-millions of dollars worth of equipment who can sit in rooms and generate this data on a daily basis as they produce their product.

DR. HENNINGFIELD: Thank you.

DR. HATSUKAMI: Dr. Burns?

DR. BURNS: Again, I'm trying to sort of refine the statement you're making to us. If the FDA decides that it needs a range of information in order to assess the concerns that might exist for the products that are currently on the market, is it your position that the small manufacturers shouldn't have to provide that data?

DR. JOHNSON: I'm not saying that they shouldn't have to provide that data. I'm saying that in some cases, because of the nature of those products, that you may already have that data, and that that data is not different from the data that you may have gotten from another source; and allowing them to access that information is one of the options available to this committee. I'm not saying that they shouldn't have to provide it.

DR. BURNS: Well, there's a couple of observations that exist that give me pause about that. One is from the Canadian experience, examining their data.

When you look at the Canadian products ranked by benzpyrene, there is one manufacturer who has a substantially elevated level of benzpyrene that is apparently, from what I'm told by our Canadian colleagues, a small manufacturer in Canada. I would think that that would be an issue of considerable concern, at least in terms of knowing it and understanding about it, for the FDA.

Secondly, it's also clear that depending on where you source your tobacco from, that you can have fairly wide variability in some of the heavy metals that are present in the raw tobacco. You identified that as an issue. And I'm assuming that you do not want the FDA to approve or have the obligation to approve each sourcing of tobacco that you make.

So I don't, again, understand why, given the economic pressures that you're under, which would include, I would expect, purchasing cheaper tobacco if it's available, how you free the FDA from the responsibility of knowing the consequences of those purchasing decisions.

DR. JOHNSON: I'm not sure I understand what your question is. I understand your comment. But I don't think that there's any implication or any intent to say that the agency is being freed from its regulatory responsibility to understand and be able to characterize products. No. I don't think that's the case at all.

I think that what I'm saying is that the tobacco selection available to small producers is very similar to the tobacco selection that's available to the larger companies as well. They don't go out and contract with a grower in some country and say, grow me some tobacco. They don't do that. They take the tobacco that's already been produced, that's already been characterized, and they use that tobacco.

Now, the agency has an obligation and the producer has an obligation. Both are obligated to make sure that the product, as produced, meets the specifications that have been set for products in commerce. And so I don't think there's anything that I said, or certainly nothing I intended to imply, that said that anybody was going to be freed of that obligation.

DR. BURNS: But you are suggesting that the small manufacturers shouldn't have to provide data for their own products uniquely that would allow the FDA to decide whether a problem exists in the quality control or the sourcing or other aspects of the products produced by small manufacturers.

DR. JOHNSON: I don't think that that was said in the presentation. But you may have gotten --

DR. BURNS: Well, I'm simply trying to clarify what your position is because I don't necessarily understand it fully.

DR. JOHNSON: Okay. I think that what was said is that the list of components that are critical components that need to be analyzed needs to be looked at, that that list needs to really be the ones that are critical to the determination of human health risk, and that that is the key list that needs to be analyzed for. And I don't think I said that there was any objection on anyone's part of being able to produce that.

I think if you look at the last bullet on this slide, it says that, "If primary components of the small tobacco product manufacturers' manufactured products are essentially the same." Are essentially the same. In other words, it's got to be shown that they are essentially the same, that you allow the manufacturers to then report based on substantial equivalence.

That's what I think is the hanging point here. I think that's what we're getting stuck on. The point is that for things you can show are substantially equivalent, that that's one approach to getting this done. There will be things that may not be substantially equivalent, and they would have to be certainly addressed. And I don't disagree with you, Dr. Burns. I think you're right. There are some things that may be different.

But for the things that are the same, that's a requirement that adds an extra burden that makes it less possible for the small producers to do those things that allow them to generate the data for those unique product attributes, product-attributable components, that are of significance to the agency and are significant to the regulatory process.

DR. BURNS: I mean, there's no question that if you know that they're the same, then you can assume that they're the same. The problem is how you go about the process of knowing that they're the same.

DR. JOHNSON: Well, I don't disagree with you, and I think that there are processes in the agency that allow you to define that. Those processes exist on the pharmaceutical side on a routine basis as you start to think about the difference between ethical and generic products. How do you show that those are equivalent products so that the generic can now be sold in the marketplace? That same process is a process that has a reasonable application here, I think.

DR. BURNS: I certainly would agree with that because it's a process based on testing.

DR. HATSUKAMI: Dr. Lauterbach?

DR. LAUTERBACH: Yes. Dr. Burns, in the legislation, there are provisions recognizing essentially the difficulties of the smaller manufacturers. And Congress specifically gave them more time and additional delays if there's not sufficient capacity. But I just want you to know that Congress did recognize the plight of the small tobacco manufacturers in this case.

DR. BURNS: No one is arguing that there aren't process issues. Our task here on the committee is to define the content, that is, a list of constituents. And the question I was driving towards is whether or not you believe that the small business manufacturer should be exempted from providing a list of those constituents, or have those considerations by the FDA not apply to them, or whether you were saying something else. I simply wanted to understand what the position was.

DR. HATSUKAMI: I don't think, Dr. Johnson -- you didn't say that the small manufacturer should be exempt from --

DR. JOHNSON: No, I did not. No.

DR. HATSUKAMI: All right.

Dr. Henningfield?

DR. HENNINGFIELD: No.

DR. HATSUKAMI: Any other clarifying questions?

[No response.]

DR. HATSUKAMI: Thank you.

I'm going to ask the subcommittee what they would like to do. We can either break for lunch at this point in time or we can start our discussion on the criteria by which we should be selecting harmful or potentially harmful constituents.

DR. TEMPLETON-SOMERS: I'd like to ask that anybody who is a registered speaker for the open public hearing be sure to sign it at the desk if you have not because we may be moving that time up a little. Thank you.

DR. HATSUKAMI: Any strong feelings one way or another? All right.

Dr. Husten?

DR. HUSTEN: Yes. If you're going to get started, several of the presenters raised questions of the purpose of the list, and so I'd like to reiterate the purpose.

So what we're asking the subcommittee to do is specifically help the FDA in terms of our statutory requirement to establish and periodically revise, as appropriate, a list of harmful and potentially harmful constituents, including smoke constituents, to health. We are required to publish this list, including quantities present by brand and sub-brand. We would encourage the committee not to stray beyond that purpose. That is the purpose of the list, and we're asking the committee to stick to that purpose.

DR. HATSUKAMI: Any questions from the subcommittee?

Yes, Dr. Burns?

DR. BURNS: This is one of the questions I had coming in. So the list we come up with is going to go to the parent committee. The parent committee will send it to you guys, and you guys will do something with it, to accept or reject some of the components of that list based on the advice you provided.

But once that's done, then you're obligated to receive from the manufacturers quantities of each of those constituents by each brand.

Is that right?

DR. HUSTEN: We are required to publish the list, including quantities by brand and sub-brand.

DR. HATSUKAMI: Dr. Henningfield?

DR. HENNINGFIELD: And this is maybe a question for the FDA. In the last presentation, implicit was a plea that the committee not make recommendations that hurt small manufacturers, and I'm paraphrasing, and process issues and capacity and how much money they have and scientists they have were raised.

I guess, as somebody serving on the advisory committee, I don't understand that that is any part of our charge, or is it? My understanding is that our charge is to look at the science, the potential public health effects. I assume feasibility at some level, as flows from the science, has to be there. But should we be considering whether or not a small company can do something or a big company only can do it?

DR. HUSTEN: What we're asking you to do is develop a list of harmful and potentially harmful constituents, identify why those constituents should be on such an initial list, and if there are methods to measure those; and then as we get into the second meeting, a more detailed discussion of what those methods might be. That's the charge.

DR. HATSUKAMI: Dr. Farone?

DR. FARONE: Harmful and potentially harmful. To me that sounds like two lists.

Is that the intent, I mean, to know which things are considered to be harmful and which things are in another class that may be potentially harmful that maybe don't have enough information or something?

DR. HUSTEN: We're asking the subcommittee to make recommendations on a single list, given the fact that there may not be every single time point from a constituent to proven it causes a specific disease. So it's a single list.

DR. FARONE: Okay.

DR. HATSUKAMI: Any other questions?

Yes, Dr. Burns?

DR. BURNS: In some of the materials we got, and certainly in the presentations from the industry, the issue of prioritization came up. And is that part of our charge or not?

DR. HUSTEN: We're asking you to develop the criteria. We are not specifying for you any particular criteria for selection. That's part of your charge, is to talk about what might be appropriate criteria for this initial list.

DR. BURNS: Well, but specifically, the question is in that list, you want a list of all those constituents that we believe to be harmful or potentially harmful. Are you asking for any kind of prioritization on that list, or are you simply asking for the list without regard to prioritization and a set of standards by which the risk could be assessed for those constituents?

DR. HUSTEN: We're asking you to develop criteria and a list. We're not asking you to specifically order a list.

DR. HATSUKAMI: Any other questions regarding the purpose?

[No response.]

DR. HATSUKAMI: Well, maybe what -- oh, I'm sorry.

Yes, Dr. Watson?

DR. WATSON: Sorry. It's my understanding -- maybe we could get clarification here -- that any list we develop today could be modified in the future. And so I would think we would want to use sort of the best science available to come up with a list. But obviously, the list might change over time as the science evolves.

DR. HUSTEN: This is an initial list. And yes, the statute specifically says that it can be revised as necessary.

DR. HATSUKAMI: Dr. Djordjevic?

DR. DJORDJEVIC: Just one more clarification. Are we going to have one list for tobacco and one for tobacco smoke, or it will be again only one list?

DR. HUSTEN: I think the committee's going to have to look at the evidence that's out there and see if it makes the most sense to have a single list or to break it up. We had not specifically charged the committee with coming up with separate lists.

DR. HATSUKAMI: Any other questions?

[No response.]

DR. HATSUKAMI: Well, maybe what we should do is we should begin.

Our first charge is to have a discussion on the criteria for determining the initial list of harmful and potentially harmful constituents. And certainly we had some presentations today that discussed different criteria for selection.

So I will open the -- maybe what we should do is we should first -- what we need to do is we need to identify carcinogens, toxicants, and addictive constituents. And perhaps what we should do is start off with thinking about identifying harmful and potentially harmful constituents related to carcinogens, thinking about what criteria we should consider to identify those harmful constituents.

So I will open up the committee for discussion regarding that.

Dr. Hecht?

DR. HECHT: We have structured evaluations by IARC and the U.S. government Report on Carcinogens that takes into account all of the available published data from studies in animals and studies in humans, as well as mechanistic data. So I don't think we would want to repeat that.

My suggestion would be that we simply accept their evaluations and use those evaluations as a basis for the list. In the case of the IARC, groups 2A, 2B, and group 1 should be on the list.

DR. HATSUKAMI: Dr. Burns?

DR. BURNS: I would second that, with the one caveat that the group should formally review procedures by which IARC makes those designations and confirm that they agree with those, simply so that we have the opportunity to consider the basis under which our decision for inclusion of all of those compounds on the list was made.

I don't see it as a substantive, time-consuming exercise. Simply sending out the -- and the IARC has a very structured set of criteria -- sending those out to the committee members, sending out the U.S. government criteria, and then, at the next meeting, we can simply have a short discussion that says those are acceptable criteria.

But I think, as a matter of developing this list, we ought to be clear that we both specify the reasons for inclusion and what's included rather than simply saying that we adopted the Hoffmann list or the IARC list or some other list.

DR. HATSUKAMI: So what you're suggesting, then, is in the next meeting we should have a little bit more detailed discussion. We can adopt that we would -- we can say that we will adopt the IARC criteria, but we should have some discussion on it at the next meeting.

DR. BURNS: Yes. Just send out the printed matter for the IARC criteria and for the U.S. government criteria, and then we would be in a position, then, to say we have reviewed that and think it's appropriate.

DR. HATSUKAMI: Yes.

Ms. Jinot?

MS. JINOT: I also agree with that, that we shouldn't re-duplicate efforts that have been made by other agencies. And I would just add to the list of U.S. government reports not just the Report on Carcinogens, but that the U.S. Environmental Protection Agency also classifies carcinogens. And we have guidelines that are similar to those used by IARC and by the National Toxicology Program. But we may have looked at different chemicals, so there might be advantages to including that as well.

DR. HATSUKAMI: Dr. Farone?

DR. FARONE: Well, generally I agree with that. There are some cases where there are chemicals that are on different lists that are listed as carcinogens that don't show up on those.

So I would say that is primary, but that's why I previously asked the question about the potential things that -- I don't -- I have to use examples, I'm sorry, but like pyridine. Okay? I mean, it is classified by some people under some criteria as being a carcinogen, like in California. It doesn't show up, I don't think, on the IARC list.

But potentially it may be something that one would want to include on that list in addition to maybe something that has to do with -- as a central nervous system compound that does affect that, could have something to do with addictive properties.

But I'm just saying there are going to be some questions, and I think those are where we might want to focus our attention on whether or not those questionable things end up on the list for one or another reason.

DR. HATSUKAMI: So, Dr. Farone, so pyridine is not on the IARC list. And why is that? Are there some criteria that were used?

DR. FARONE: Yes. California uses the 1 in 100,000, and they have it reviewed by a separate group of toxicologists and biochemists. And I'm not quite sure of that; that was one thing I didn't have time to check before I came in. It's on, of course, the

Hoffmann original list. It's not on the 44 -- well, it may be on the 44 analyte list. I didn't check it completely.

But it is a compound of interest that has been implicated, at least as I can find from the literature, starting in 1896, as being somehow involved in the smoking behavior because of its CNS activity being so strong.

However, if we're talking about carcinogenicity list, I don't know whether to include it or not. I do know in California they include it. I don't see it on many other lists. But I think this is one of those cases where we could look at the criteria. For example, I'm not sure it's on the EPA criteria.

Some of the things are listed, at least in California, as only being inhalation carcinogens. So then you have the issue of, okay, it's on the list for cigarettes, but it may not be quite as important for a smokeless product.

But I'm just thinking in general. I mean, I agree with everything that's been said. That's obviously the gold standard, and we start there. But how do we then include these other materials?

DR. HECHT: Well, we -- sorry.

DR. HATSUKAMI: Dr. Heck and then Dr. Hecht.

DR. HECK: I do think our discussion here has to start somewhere. And let's all bear in mind, though, in terms of the ultimate goal of this committee, the subcommittee, and the larger committee, and indeed ultimately the FDA's purpose, in providing this list, let's bear in mind that various lists -- and we heard the NTP list mentioned -- are configured for different reasons. We have entities like saccharin, for instance, has been on again/off again, not off again, justifiably, the NTP list of carcinogens.

We have to keep in mind, too, some of the points that were made this morning. The very real, practical considerations of the availability of sound, validated methods of quantification at levels found in the milieu of cigarette smoke, this is going to be a very practical consideration ultimately for the regulatory purpose of this list.

Let's bear in mind also the levels of these constituents found in smoke. I think there are some constituents -- nickel compounds, for instance, possibly an example -- that although found in smoke in some analyses at some level, really are probably not reasonably considered to be prime contributors to the human diseases caused or associated with smoking.

So let's try to reasonably filter these lists for the benefit of the committee, and the FDA ultimately, to the extent that we can scientifically.

DR. HATSUKAMI: Dr. Hecht?

DR. HECHT: There are some constituents of carcinogen lists that have been published that are not routinely analyzed and that could be in extremely low concentrations or possibly aren't even present. So that has to be taken into account.

The other thing is that in looking at the IARC list, maybe there are constituents that IARC simply hasn't evaluated that need to be on our list. So I think we should use IARC and the Report on Carcinogens as a starting point, but that it shouldn't necessarily be exclusive because there may be compounds that are important that IARC hasn't gotten to or NTP hasn't done yet.

DR. HATSUKAMI: So what kind of criteria would you suggest to select those compounds, Dr. Hecht? If you're saying that there may be some that haven't been identified by IARC, is there a particular criteria that we could use --

DR. HECHT: Yes. But there may be data in the literature that indicate that these compounds are important. One that comes to mind is naphthalene. I'm not actually sure whether IARC has done naphthalene or not, but there's data from the NTP studies that indicates that naphthalene is carcinogenic. And there's a significant amount of naphthalene in cigarette smoke.

I'm just saying we have to be careful not to ignore something that might be important just because IARC may not have done it yet or NTP may not have done it in the Report of Carcinogens.

DR. HATSUKAMI: Dr. Burns?

DR. BURNS: I would, to a certain extent, agree with Steve. And in that setting, the only obligation -- the only way that we can do that is, obviously, if nobody else has reviewed it using the appropriate criteria, then we would have to conduct some form of independent review to decide whether it's on the list or not.

We could have adopted the IARC criteria for conducting that review, but we would still have to review it, which raises a question of, again, a process that I think we need to make a decision on so that we can hopefully shorten this up a bit.

All we need to do is identify whether it's on the list. We don't need to -- and we need to identify some criteria for having been on the list. But if, for example, in acetaldehyde, which is listed for all of them -- cancer, non-neoplastic respiratory disease, cardiovascular disease, and addiction -- do we need to go through -- having identified it for cancer, do we need to then conduct another review for non-neoplastic disease and another review for cardiovascular disease and another review for addiction, or once it's on the list, and it made the list because IARC had reviewed it as a carcinogen, do we need, then, to add those additional specificities or not?

Because for the others -- for cancer, it's relatively straightforward because a lot of groups have done it. But for some of the others, there aren't organized groups that have established criteria that have conducted reviews of a lot of these substances. And so we're going to have to come to grips with actual data that's published and then review ourselves. And I don't know that we have the time and resources to accomplish that.

DR. HATSUKAMI: Dr. Husten?

DR. HUSTEN: We're asking you to develop a list of harmful and potentially harmful constituents. So if you have a reason to put something on the list, I'm not sure the committee needs to go into exhaustive detail about all the possible reasons it might be on the list, if you have what you consider to be a sufficient reason.

Obviously, we can go through and explore are there other issues. I think your charge is really to tell us what constituents should be on the list and have some sort of rationale for why they're on there.

DR. HATSUKAMI: Any other comments?

[No response.]

DR. HATSUKAMI: So what I'm hearing, basically, is that we should adopt the IARC criteria as well as the U.S. government criteria, that that's where we should start is adopting their criteria for identifying carcinogens.

However, there's a possibility that there are carcinogens that are not listed by IARC or the U.S. government that we should be open to, and that we should base that upon review of the literature. That essentially fulfills the criteria that has been established by IARC. Right?

Is that what you're saying?

Dr. Hecht? Did I interpret --

DR. HECHT: I don't know if we can do an IARC type of review. I mean, an IARC review is extremely thorough and quite time-consuming and expensive. But there may be data out there from respected laboratories that indicate that a given constituent should be on the list, and --

DR. HATSUKAMI: Sure. So use the IARC criteria to identify some of those constituents, is what you're saying. We don't have to do --

DR. HECHT: The IARC criteria are extremely structured. Okay? I don't think we have the resources to do an IARC type of review. But we have to take into account the data that are out there.

DR. HATSUKAMI: Any other additional comments?

Dr. Farone?

DR. FARONE: Yes, Dorothy. Using again my example, I mean, we can get all the literature that caused the state of California Department of Health Services to put pyridine on the list. We can look at that literature and see whether it's the same, whether it's different. And that would be the same for EPA analysis of things. In other words, when these other analyses are done, there's a report and there's a body of literature associated with that.

So I think what Dr. Hecht is saying is very reasonable. We get a hold of that set of information and we look at it and we see whether or not that's enough information to convince us that it's close enough that it should be on the list.

DR. BURNS: Because again, we're freed of the IARC responsibility. We don't have to define it as a proven carcinogen. We have the opportunity to say that it is hazardous or potentially hazardous. And if the review is -- as Bill says, if the review suggests that it's probably hazardous, then potentially it can be included.

DR. HATSUKAMI: Dr. Heck?

DR. HECK: I think, maybe to reiterate a point I tried to make earlier, our compilation here, if it comprises just basically an assemblage or stapling together of existing lists, is going to look pretty much like everyone else's. It's going to be extensive, numbering in the dozens or scores.

The best thing we can do is, at this subcommittee level, to the extent we can, as I think Dr. Burns or Dr. Hecht mentioned earlier, we are empowered to use our scientific process here to list entities that may not have been listed by IARC or others if we feel there's a scientific basis for their inclusion in the particular instance of cigarette smoke exposure.

Let's empower ourselves as well to be judicious in filtering these massive lists that are assembled internationally for a variety of reasons which may have more or less applicability for our special circumstance here. I think the full committee would be well served if we can provide a modest-sized targeted list of, arguably, the most significant constituents.

That list can always be expanded for any number of reasons subsequently. But if we simply provide a world inventory of whatever portion of these 8,000 constituents of smoke is available, I think we're not going to really do much to advance the full committee and ultimately the FDA's purposes here.

DR. HATSUKAMI: Comments from the subcommittee?

DR. BURNS: Well, I thought that was specifically what we were told we couldn't do. We have not been tasked with defining which ones are the high priority ones. I mean, our task is to define which ones are hazardous and potentially hazardous. And so, absent a change in the charge, I don't see how we get to a list of the top five or something that would meet your needs.

DR. HECK: But I think implicit in that charge is a degree of judgment as to the presence in smoke, the levels in smoke, and, explicitly stated or not, a degree of scientific confidence that a particular entity is indeed significant.

We all know there's literature that argues, on the basis of traditional risk models, that benzo[a]pyrene, for instance, is not likely a significant contributor to lung cancer risk from smoking. The same risk weighting schemes rank NNK, for instance, fairly low.

Now, I think this committee needs to step beyond all these efficient tools we have and, to the extent we can, provide some additional insight. I think there may be other reasons that benzo[a]pyrene and NNK should presumably be listed on such a list. So let's empower ourselves to apply as many of those judgments as we can at this stage because the full committee's going to be faced with these same questions and a short period of time, and the more progress we can make at this stage, I think it'll be good.

DR. HATSUKAMI: So basically what you're saying is that we should not just take into account that a particular constituent is a carcinogen, but also take into account the level of exposure.

DR. HECK: To the extent we can, and there are other factors as well. The very practical matter of the availability of validated methods, or lack thereof for some of these entities, we have an inventory of dozens of PAHs in smoke. We don't have good, solid, quantitative methods for many of those.

Is it possible -- and this is for discussion -- that a representative PAH, for instance, would suffice to represent that class without the need to delve into the leading edge of analytical chemistry, where there are probably new PAHs being reported almost monthly? I think that would go a long way towards helping us give a useful subcommittee product to the committee.

DR. HATSUKAMI: I think one of our charges is to determine whether there is a method for quantitative assessment, right, for the constituents that are identified. So that is part of what we will be addressing.

DR. HUSTEN: Yes. One of the charges is that there are measures available.

DR. HATSUKAMI: Yes, Dr. Watson?

DR. WATSON: Just to pick up on what was just said, looking at specific chemicals on the list, benzo[a]pyrene is included because it's included as part of the polycyclic aromatic hydrocarbons, which many compounds of this class exist in cigarette smoke. Some are more harmful than others.

Benzo[a]pyrene has been widely studied as a surrogate marker for some of these other compounds. And you can argue the validity of whether or not it's a good marker or not. But is that sufficient reason to be included on the list? In and of itself, it's not terribly toxic, but it's a marker for other toxic compounds.

Can we use that as a -- or should we use that as a reason to include something on the list?

DR. HATSUKAMI: Any comments from the subcommittee?

DR. BURNS: I would certainly think so. Your other options are to get into some kind of precise quantification based on animal toxicity data and levels in smoke. And you're faced with the reality that animal toxicity data is not reliably predictive of human toxicity data on a quantitative basis, and the levels in the smoke are not predictive of the levels of exposure to people.

So I think that what we're looking for is qualitative assessments that include some consideration of how much is present, but they don't get to the point of ranking individual compounds based on animal toxicity and smoke assessment levels.

DR. HATSUKAMI: Dr. Hecht?

DR. HECHT: Does our task include mixtures? Tar, for example?

DR. HUSTEN: The definition included chemicals and chemical compounds. I mean, again, you have to -- we're asking you to determine what you think should be on the list. So we are not a priori including or excluding other than what's in the definition in the statute and our thinking about it as expressed in the guidance.

DR. HECHT: So mixtures are in, then?

DR. HATSUKAMI: I would presume so. So we could – tar.

DR. HECHT: Just used as an example. But --

DR. HUSTEN: Well, I think it's up to you to decide if it should be in or out. But the definition is chemical or chemical compound.

DR. HATSUKAMI: Yes, Doctor?

DR. HECK: To Dr. Hecht's suggestion that a mixture or quasi-defined entity such as tar may be worthy of listing, I would agree with that with reference to the previous benchmarking studies which we heard mentioned earlier.

In Massachusetts, Australia, and the U.K., we have demonstrated the utility in those different regulatory arenas of the ability of tar, a relatively well-characterized and well-validated measurement, to quite well predict the presence of a variety of other constituents of that particulate phase for which solid, validated, and adequately sensitive, or even available, methods aren't widely possible.

So there is additional value that can be obtained from a measurement or something like tar by an internationally recognized method, that we can extend that to inform a lot of other entities on this list without necessarily requiring extensive analysis for which there may not be world capacity.

DR. HATSUKAMI: Dr. Henningfield?

Oh, I'm sorry. Dr. Burns?

DR. BURNS: I'd like to express a concern about the concept of benchmarking, particularly off tar. There is no question that for most of the constituents present in cigarette smoke, there is more of that constituent present in 20 milligrams of tar than there is in 1 milligram of tar. And if you express, then, the constituent per cigarette in order -- and try to benchmark it off the amount of tar, what you get is roughly a measure of how much ventilation occurs in the filter, that is, how much the smoke is diluted in the machine measurement.

Yes, you will quantify that, but you're quantifying a meaningless number, which is the tar level on the machine measurement of the cigarette. And so when you convert that number, when you normalize it, either by per-milligram tar or per-milligram nicotine, you find substantial, very large variability in many of the toxicants present in the smoke across the brands on an individual market, which would suggest that trying to benchmark those brands by tar would lead to an imperfect and inaccurate assessment of the range of machine deliveries that would occur if they were actually measured on those individual brands.

DR. HATSUKAMI: So you're suggesting that we don't consider complex mixtures such as tar, unless we do it on a per-milligram nicotine basis.

DR. BURNS: I think that there are reasons for making the measurement of tar. And among those reasons are it allows you to quantify the mass of the smoke that is present. And that's a very valuable piece of information that allows you to normalize other constituents to it.

What I'm saying is that the process of using that value through a benchmarking process to then estimate the levels of naphthalene and benzene, and a variety of other compounds that are likely to be present based on differences between two products and their tar level, is one that would not provide us with the kind of information that the FDA would need in order to appropriately assess the concerns about the product that's on the market.

DR. HATSUKAMI: Dr. Henningfield and Dr. Farone.

DR. HENNINGFIELD: As we think about the list, I think for me, at least, it's worth thinking about different categories of substances. And there are some that are naturally occurring in the product. There are some that are formed in pyrolysis, and some that are influenced by added constituents, and acetaldehyde comes to mind. So you can get that a certain level, burning the product. You can manipulate it by the sugars and other things you add.

Then there are other things like chocolate and other added ingredients that are only there because they're specifically added to the product. And I guess this is a suggestion, not a question, unless we're advised otherwise, that we should be thinking about specific added substances.

DR. HATSUKAMI: That might potentiate the harm?

DR. HENNINGFIELD: That could potentiate the harm in the case of chocolate if we determine that there was a concern about potentiation of cancer risk or addiction risk, et cetera.

DR. HATSUKAMI: Dr. Farone, and then Dr. Lauterbach.

DR. FARONE: Dr. Watson mentioned benzo[a]pyrene, and we've talked about its relevance to the part that it plays in smoking. If you take it as a chemical and you ask what risk level you're willing to accept for being associated with it, which was what I discussed a little bit earlier, then, again, from the list that I like to refer to, if you have a risk of 1 in 100,000 at 60 nanograms per day, then it is present in cigarette smoke at a sufficient level to go above that risk.

If you ask 1 in 10,000 or 1 in 1,000, you get a different answer, of course. And I think one of the things we have to be cognizant of is that we're dealing with something -- let's take cancer -- either, depending on which number you want to use, it's 1 in 7 or 1 in 8 or 1 in 10, depending on where you are.

So our risk profile, the lower down on the risk profile you want to go, then the less of the material becomes relevant to our deliberation, or the lower level means you look for it at a lower level. And many of these carcinogens, the number that I quoted, which again comes out of the California studies, it's what that group of scientists thought. It may be greater than that. It may be less than that.

But in terms of it being potentially harmful, at least, on that list, I mean, that is a criteria. That is, it's on a list with some number that says that number that would cause the effect is lower than you would get out of two packs of cigarettes if you smoked two packs of cigarettes or one pack in a day.

DR. HATSUKAMI: Dr. Lauterbach?

DR. LAUTERBACH: Yes. I'm very concerned at these misperceptions of real chemistry of tobacco and tobacco smoke entering the discussion here. I think if we take all the American blend cigarette tobaccos in commerce, and if we put those in a common configuration and smoke them by whatever method people choose, you're going to find very, very little difference among the different commercial blends of U.S. blended cigarette tobaccos; whether they're add-free, whether they contain cocoa, whether they contain added sugars, they contain any of the normal use commercial ingredients, you're going to find very little difference among those tobaccos.

DR. HATSUKAMI: Dr. Burns, do you have a comment?

DR. BURNS: Well, that analysis has been done. It was done not, unfortunately, on U.S. cigarettes on the U.S. market because that data's not available, but it was done on the Massachusetts benchmark data and it was also done on an international sample of blended cigarettes of the U.S.

style produced by Philip Morris. In both of those instances, there was substantial variability across the individual constituents when they are normalized, per milligram tar, per milligram nicotine.

So all I can tell you is the actual observations that I've seen. Anyway, but let me make a suggestion in terms of process so that we gain ground here.

What I would suggest is a multi-step process. What we do is we take the list that we've been provided. We remove from that list nicotine, where there isn't any real question as to whether it should be on the list, and the carcinogens identified by IARC and the other agencies, and then focus our attention on the remaining items on the list to make an assessment of the information that's available.

Once that's done, then we go to an evaluation of other compounds that are not listed that perhaps should be considered for being on the list. That would give us, then, a complete list of all of the things that can be considered, and we can move from that to the question of whether there is analytic chemistry capable of making the measurements.

DR. HATSUKAMI: Yes. I would agree with that. But I think we need to also establish what kind of criteria that we're going to be using to identify those constituents. And thus far, what I've heard is that we are going to be using -- as I said before, using the criteria by IARC and the U.S. government, and possibly the one that's been developed by California.

But what I'm not really clear on is whether the extent of exposure to those constituents -- I think I heard two different opinions on that. Extent of exposure should be part of a criteria to determine whether it should be on the list of harmful or potentially harmful constituents.

So I wasn't really clear on that. Maybe I wasn't --

DR. BURNS: Well, I've got mixed feelings on that. And let me express the reason why they're mixed feelings.

One is, obviously at some level we want to be sure that the items on the list have some relationship to whether or not people are going to be exposed to them; otherwise, it doesn't make much sense that they be on the list.

DR. HATSUKAMI: Right. Right.

DR. BURNS: However, my ambivalence is colored by some recent thinking we've done on the heavy metals where there may be a reason to put something on a list for monitoring of the process, even though existing products have very low levels of them, because the potential exists, with purchases from other countries or different products, to substantially alter that.

If you're really interested in monitoring the levels of those that are occurring, then there may be a reason to put it on the list even though, for example, some of the heavy metals on the Canadian list, most of the cigarettes don't have any measurable quantity of them.

DR. HATSUKAMI: Any response to that?

DR. HECHT: If it's on the list, people will develop the necessary analytical chemistry. That's my belief. So I don't think we should be that concerned initially whether the methods are available because methods can be developed for -- good methods can be developed for, I think, most of the things that we're going to think of.

DR. HATSUKAMI: Dr. Lauterbach?

DR. LAUTERBACH: Dr. Hecht, as one who's headed up the methods development group for a major tobacco company, I tend to agree with you. Given unlimited resources, all the fancy instrumentation you want, yes, you can do those things. But the point is that can they be done in a commercial laboratory situation, not in a research situation?

DR. HATSUKAMI: Dr. Farone?

DR. FARONE: Yes. Well, nickel was mentioned, and I just want to point out there's various forms. And one reason for including the metals is that the forms that you're most likely to encounter in smoke -- for example, nickel carbonyl -- is a little bit more serious form than nickel metal. The amounts are different.

So I think when we consider the metals particularly, where the compound produces a well-known carbonyl or something that is likely to occur at a reasonable level by combustion or pyrolysis, then to me that is a reason, from an exposure point of view, of including it on the list.

DR. HATSUKAMI: Ms. Jinot?

MS. JINOT: Yes. I like Dr. Burns' approach of how we might proceed. And in terms of criteria, I mean, it seems that the lists we've been given to look at largely are things that are fairly established for carcinogenicity and other types of toxicity. But with so many chemical constituents, a lot of things haven't been tested. And there's where it might be important to have some exposure information to know -- like we can't, obviously, look at 8,000 constituents. So at some level, we might have to look at the ones where we don't -- I'm sorry.

For example, using the IARC criteria of 1, 2A, and 2B, that requires that there be bioassay data, so rodent data where carcinogenicity has been tested for, or a high level of mechanistic data. But as a screening level, we might also be concerned about things that are known mutagens or have structure/

activity relationships with chemicals that have known types of toxicity as well as a way of getting at some of these that may not have the full amount of testing for reproductive toxicity or for carcinogenicity.

So I guess I'm concerned about, yes, some of those that aren't on the lists already, but it may just be because they haven't been tested or haven't been as fully tested as the ones where we have the full bioassay data or something like that. So I think we do need to look at some of the other -- of screening types of test in considering criteria.

DR. HATSUKAMI: Thank you.

Actually, after this one question, I think we should break for lunch because I think it's time. So Dr. Watson, and then we'll continue the conversation.

DR. WATSON: I just wanted to second something Dr. Burns said a minute ago about when you're looking at things and smoke, that it may not be a problem at the moment but are of concern, things like heavy metals, for instance. And we've seen today by the very nice talks that were put on by the tobacco industry -- it really was very interesting -- learning how global tobacco really is, and that if tobaccos are coming from other regions of the world, where if, say, one were trying to establish performance guidelines, took a big sampling of current cigarettes on the market, and then used that as a basis for setting guidelines, that might only capture a small snapshot of what's available.

Particularly for regions of the world where metals like cadmium and lead are very high, you might miss those. So those might get underreported in the current level of testing of analysis when you're trying to make decisions.

We need to be sort of aware of this. And it really is -- it's not just a U.S. market we're concerned about. I mean, it is products sold in the U.S. market, but the tobacco is coming from other places in the world. We need to be aware of that and what potential levels of constituents might be in those tobaccos.

For instance, we know that in different regions of the world where Virginia tobacco is predominant, there's a difference in the contributions from the nitrosamines and the PHs (phonetic) as opposed to American blended cigarettes.

So I think all these considerations need to go in account in our recommendations. There could be variations, and taking a snapshot view might not be representative of what's happening globally.

DR. HATSUKAMI: Thank you.

All right. I think we're going to go ahead and break for lunch, and I have to read a few things before we do that, or a few reminders here.

Committee members and consultants, you have to please remember that there must be no discussion of the meeting topic during lunch, either amongst yourselves, with the press, or with any member of the audience.

So with that, I think we could go. We'll reconvene in this room in one hour, about -- so at 1:00. We'll reconvene at 1:00 p.m. Thank you.

(Whereupon, at 12:02 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:07 p.m.)

DR. HATSUKAMI: I think we're going to get started here.

So before the lunch break, we had identified the criteria by which we wanted to choose harmful and potentially harmful constituents for carcinogens. And what I'd like to do now is to go over the list of the carcinogens established by IARC and NTP, and I want the subcommittee to indicate whether they think that the carcinogen should or should not be on the list.

I think, Karen, you have the --

DR. BURNS: Based on the criteria of IARC and NTP.

DR. HATSUKAMI: Yes. Based on the criteria of IARC and NTP.

So again, what we're going to do is we are going to go through this list. This is the list that was established by NTP and IARC. And the subcommittee is going to decide whether they should be included on the list of harmful or potentially harmful carcinogens.

So we'll start with the first constituent. So the first carcinogen is 2-aminonaphthalene. Sorry, I'm not a chemist. And Steve Hecht, even though we've been collaborating for a long time, we don't talk about this constituent too often.

DR. BURNS: How about reading off the names?

DR. HATSUKAMI: Oh, that's a good idea. Why don't we do that. All right.

So are there any objections in terms of having this particular constituent on the list?

DR. LAUTERBACH: Excuse me. We're looking at this without levels in smoke or tobacco in front of us. And I think we really need to have a full data set in front of us to make a decision.

DR. HATSUKAMI: I think our task right now is to identify whether this is carcinogenic or not, whether we consider it to be a harmful constituent or a potentially harmful carcinogen.

DR. LAUTERBACH: You mean at levels typically found in tobacco products or in cigarette smoke?

DR. BURNS: As a qualitative statement, the first step in the process is to identify whether or not the substances have been identified as carcinogens. We then have several subsequent steps in the process before they make it onto a list. This is just to assemble compounds that have been identified as, A, present in cigarette smoke, and B, carcinogenic. We'll then go through subsequent steps to find out whether it's reasonable to put them on the list.

DR. HATSUKAMI: This is an initial first step in terms of identifying those constituents.

Yes, Dr. Heck?

DR. HECK: And I might request, just for the purposes of this provisional discussion here, when we get to the inorganic elements here like cadmium, for instance, or nickel, we had some discussion earlier about different forms of nickel, and indeed, IARC and other authorities do make distinctions.

So for the purposes of this discussion, can we agree that we're talking about just elements here, like cadmium, nickel, chromium, as opposed to nickel subsulfide, nickel sulfide, nickel oxides, metallic nickel, et cetera, as elements?

DR. HATSUKAMI: Okay. So we'll start off with the first constituent.

Are there any objections to having that on the list?

[No response.]

DR. HATSUKAMI: If not, we'll go on to 4-aminobiphenyl.

[No response.]

DR. HATSUKAMI: No? Inorganic arsenic?

[No response.]

DR. HATSUKAMI: Benzene?

[No response.]

DR. HATSUKAMI: Benzo[a]pyrene?

[No response.]

DR. HATSUKAMI: 1,3-butadiene?

[No response.]

DR. HATSUKAMI: Cadmium?

[No response.]

DR. HATSUKAMI: Chlorinated dioxin?

[No response.]

DR. HATSUKAMI: Chromium?

[No response.]

DR. HATSUKAMI: Nickel compounds?

[No response.]

DR. HATSUKAMI: 4-(methylnitrosamino)-3 -- NNN, or NNK? Sorry.

[No response.]

DR. HATSUKAMI: NNN?

[No response.]

DR. HATSUKAMI: Next.

Yes?

MS. JINOT: Formaldehyde, I believe, according to IARC, should be on the previous list, the known human carcinogens. Formaldehyde.

DR. HATSUKAMI: Okay. It's noted.

Any objections?

[No response.]

DR. HATSUKAMI: What about the other two constituents?

[No response.]

DR. HATSUKAMI: Is that it?

Steve, can you read those?

DR. HECHT: Nitrosopyrrolidine and

nitrosodimethylamine.

DR. HATSUKAMI: And these are considered possible human carcinogens. Acetaldehyde?

[No response.]

DR. HATSUKAMI: Acrylonitrile? Nitrite, I'm sorry. Nitrile, I'm sorry.

[No response.]

DR. HATSUKAMI: Catechol?

[No response.]

DR. HATSUKAMI: Cresols?

[No response.]

DR. HATSUKAMI: Crotonaldehyde?

[No response.]

DR. HATSUKAMI: No? Isoprene?

[No response.]

DR. HATSUKAMI: Lead?

[No response.]

DR. HATSUKAMI: Mercury?

[No response.]

DR. HATSUKAMI: And styrene?

[No response.]

DR. HATSUKAMI: Now there are ones that were listed on the summary list that you all received that were not on this list that we presented right now. And I guess the question is whether we should include them or not.

So the ones that were not listed on the PowerPoints that we need to consider are 1-aminonaphthalene.

Any objections to including that on the list?

[No response.]

DR. HATSUKAMI: No?

DR. BURNS: Just for the record, that's included on the Brazil --

DR. TEMPLETON-SOMERS: Microphone.

DR. BURNS: That's included on the Brazil and the Canadian and the Australian and New Zealand reporting lists, I think.

DR. HATSUKAMI: Yes.

DR. BURNS: Not on New Zealand, but on the other three.

DR. HATSUKAMI: Hydroquinone? Any objections to that?

[No response.]

DR. HATSUKAMI: Mercury?

DR. BURNS: Mercury was on --

DR. HATSUKAMI: Oh, I'm sorry. Mercury is checked. I'm sorry.

N-nitrosoanabasine?

[No response.]

DR. HATSUKAMI: Phenol?

[No response.]

DR. HATSUKAMI: N-nitrosoanatabine?

[No response.]

DR. HATSUKAMI: No? No objections?

DR. HECK: I think that this may be a discussion for later. But the minor alkaloids, NAB and NAT, and Dr. Hecht can certainly comment on this knowledgeably, I think the evidence for their carcinogenicity is far less compelling than that for the major nitrosamines, NNK and NNN.

Dr. Hecht, I don't know if you --

DR. HECHT: Yes. That's correct. There is evidence of carcinogenicity of nitrosoanabasine but not nitrosoanatabine. So there's really no reason to have nitrosoanatabine, if this is a carcinogen list. And I've forgotten --

DR. HATSUKAMI: So now --

DR. HECHT: -- what the IARC rating for nitrosoanabasine is. It's probably 2B.

DR. HATSUKAMI: So what you're saying, Dr. Hecht, is to include nitrosoanabasine but not nitrosoanatabine?

DR. HECHT: Right.

DR. HATSUKAMI: Any concerns or objections on that?

[No response.]

DR. HATSUKAMI: All right. The other compounds included -- quinoline?

DR. BURNS: I thought you said that.

DR. HATSUKAMI: That's what I thought, too.

DR. LAUTERBACH: Could we have the chart up on the board, please?

DR. TEMPLETON-SOMERS: Well, just a minute. We're trying here. This is the chart but it doesn't have our notes on it yet because we've been scribbling -- I believe that we have them all included so far.

Was there a decision on hydroquinone?

DR. HATSUKAMI: Hydroquinone?

DR. HECHT: Yes.

DR. HATSUKAMI: Yes. And I think we covered everything else on this list. 3-aminobiphenyl, I guess, is -- I thought we had that covered, did we not?

Well, just in case we didn't cover it on the previous list, that'll be 3-aminobiphenyl. I believe we approved that as a carcinogen.

DR. HECK: I think that in case of 4-aminobiphenyl, there's an arguable reason to list that, but 3-aminobiphenyl, I don't think, is as compellingly linked to cancer.

DR. HATSUKAMI: So not 3-aminobiphenyl.

I guess the last constituent that we did not discuss was tar.

Is that something that we want on the list of --

DR. BURNS: Which one?

DR. HATSUKAMI: Tar.

[Pause]

DR. BURNS: I agree with tar.

DR. HECK: I might add, just a comment here, that in terms of the listing of TCDD or dioxin-like compounds, as they're commonly termed, there have been -- the literature has varied over the years, with some reports reporting that class of sometimes poorly characterized entities in smoke, and other reports have not seen that. So let's remain open to the possibility that some of these entities may not in fact be routinely and reliably detectable in smoke.

DR. HATSUKAMI: Noted.

All right. So let's go over the constituents again. I want to make sure we got them all. So, basically, Karen, what you did is you checked the ones that we approved to be included as harmful or potentially harmful.

So does this include the IARC list, then, too? Yes?

Yes?

DR. HECHT: I've gone through the IARC monographs and through the recent literature. And independent from work for this committee, I prepared a list of compounds that have been analyzed in tobacco smoke and that are either in group 1, 2A, or 2B.

I have a lot of compounds that are not on your list. I've got 72 compounds.

DR. HATSUKAMI: That are not on our list.

DR. HECHT: Not 72 that are not on your list, but I have quite a few that are not on your list. So I think we should discuss these at some point because I think your list is quite incomplete.

DR. HATSUKAMI: So, Steve, how many compounds were not -- do you know how many were approximately not on your list? And at this point --

DR. HECHT: I would say there are at least 30. I mean, I didn't count them, but --

DR. LAUTERBACH: Yes. Dr. Hecht, is there any way we could get that list over to the business center and have some copies made so we could discuss it? We may agree with you on some.

DR. HECHT: Yes. You might.

DR. HATSUKAMI: I think that's the best -- so why don't we do that. Why don't we have someone copy Dr. Hecht's list.

Yes, Dr. Farone?

DR. FARONE: Yes. As part of the information for the meeting, you sent out part of Volume 83 of the IARC monograph on Tobacco Smoke and Involuntary Smoking, and many of the compounds that I'm sure are going to end up there are on the list associated that was sent out as part of the IARC.

For example, there's, it looks like, 12 polynuclear aromatic hydrocarbons, and there's five heterocyclic hydrocarbons. So I presume we're going to find them on Steve's list, but they're on the information that was sent out. That's the monograph 83 from IARC, which has two pages of lists of carcinogens in cigarette smoke.

DR. HATSUKAMI: So I think what would be really helpful is if we could have this list -- people have it available, but not everybody has it available. If there's any way that we could try to combine what we have already approved, what's missing from Steve's list, and what's missing from this list, I think that would be most useful because it's hard to keep track of what we've already --

DR. HUSTEN: We can help with that while you guys are talking.

DR. HATSUKAMI: Why don't we do that.

So I think the best thing to do is why don't we move on to the next set of criteria that we need to determine, and that's for toxicants. While we're waiting for the list of carcinogens, I think we should go ahead and move on to the toxicants. And so these would be constituents that may be related to non-cancer. So they would be the non-neoplastic respiratory effect, the cardiovascular effect, and addiction.

So why don't we start off with trying to consider the criteria. Yes?

DR. HUSTEN: Dorothy, some of these are also on the carcinogen list because we did not -- we just copied the checks.

DR. HATSUKAMI: Right. Right.

DR. HUSTEN: So some of them have already been approved, basically. I wanted to point that out.

DR. HATSUKAMI: Right. Yes. So we don't

want to repeat that.

So let's first talk about the criteria by which we want to choose or identify these constituents. I know the criteria that have been used by Fowles and Dybing was the hazard index. And just to open up for discussion, are those the criteria that we should consider to identify the non-cancerous constituents?

Thoughts? Yes, Doctor?

DR. BURNS: Well, I think to be clear, Fowles and Dybing used that same hazard index for different inputs, but the same hazard index concept for carcinogens as well.

DR. HATSUKAMI: Right. Right.

DR. BURNS: And I think what they used for the non-neoplastic effects was measures of irritant or inflammatory response. And so one of the things that I think might be helpful for us would, A, be to dispense with the concept of non-neoplastic respiratory effects and specify what we're talking about, which is inflammation, oxidative stress, and whatever else is out there, and then look at what EPA and the other folks have done to evaluate individual compounds.

Certainly, for air pollution, irritation is a major toxic measure that they use. And so it would be helpful to know what specific kinds of criteria they use, and then, when they apply those criteria, how they have been applied to the compounds in tobacco. Then we can get into whether the levels of those compounds are sufficient, with some kind of toxicity or hazard index, to merit inclusion on the list.

I'm a little reluctant to simply --

DR. HATSUKAMI: Come up with a criteria?

DR. BURNS: -- assume that we have COPD criteria and list them as causing COPD when, at least in my reading of that literature, it's unlikely that most of the substances we're going to put on there have an end organ measure of COPD as the metric that is used to assess them as being toxic.

DR. HATSUKAMI: So really, so not to use end organ as a criteria so much as looking at criteria such as inflammation and oxidative stress.

DR. BURNS: We're not alone in this. When you look at people who are looking at air pollution measures, they are concerned about chemical toxicities that would influence and damage the lung. And I believe that what predominately they use are measures that would create inflammation, and to a certain extent, things that cause oxidative damage.

Those are things that have easier metrics in the laboratory than trying to generate a picture in an animal that looks like COPD in people as the metric by which you assess the toxicity of a product. I mean, they've done that for cancer because cancer grows in the animals.

DR. HATSUKAMI: Right.

DR. BURNS: But the animal models for heart disease and lung disease are not as robust.

DR. HATSUKAMI: Yes?

DR. HECK: Just one additional comment, following onto what Dr. Burns has offered here. I'd offer a cautionary note in that we know that essentially all substances are toxic or hazardous or may convey some risk at some level of exposure.

We have some instances on this list -- if we tie this provisional list that we are about today that will be presented to the committee subsequently for, in some fashion, prioritization for regulatory scrutiny, if we tie our provisional listing here to -- or attempt to tie it too much to mechanisms, to availability of documented dose/response studies, we're going to find that many of these entities really do not have sufficient dose response studies or toxicology quantitative-type studies where we can with confidence tie them to a mechanism.

I see, for instance, eugenol coming up on this list. And we see on the list that was provided to us some suggestions that eugenol may be responsible for effect XYZ. If we really look at the hard data available for that, we may find it inadequate to support some of these more mechanism-based lists that I think ultimately will have to be considered by the full committee.

So if we are here just incorporating by reference other authoritative lists of carcinogens or toxins or whatever, fair enough. But I think we or this committee subsequently will at some point really have to look into the literature on each of these materials, and we may find it rather thin in some cases. Other cases, risk estimates were developed from oral studies, let's say, or even topical studies and not from inhalation. So we're going to have some difficulties in tying those with confidence to the respiratory health effects of smoking.

This is exactly the sort of difficulties this industry has been wrestling with for five decades now, really trying to go through this bewildering list of constituents and figure out which ones really should be prioritized for reduction or elimination.

DR. HATSUKAMI: Right. So it's a really difficult task before us. And I guess maybe the best way to approach this is to take a look at the list that other countries and agencies have identified, and then decide from there.

I mean, basically, each of these, the lists were developed with specific criteria in mind. And I guess maybe the best thing to do is decide whether the constituents should be part of the list or not part of the list, and then just go from there.

Do you think that that's the best process at this point in time?

DR. BURNS: Well, I think it might be useful to examine how other folks have set criteria before we -- because I think with many of those lists, there aren't -- for instance, the Canadian list doesn't have a specified designation as to why something's on there. I mean, it's on there because it's bad, but they didn't go through the process of enumerating why they thought it was bad. Basically, my impression is that many of the lists come from the Hoffmann list. They just sort of adopted most of the things on the Hoffmann list that they could measure and put that out as a list.

So EPA and other folks who deal with lung disease and heart disease risks have developed some methods by which they make assessments. And it would be useful to know --

DR. HATSUKAMI: What those methods are.

DR. BURNS: -- what those methods are and what they have found for some of the specific compounds. That will give us a more informed view of whether or not the compound should be included on a list of potentially toxic substances, and then we can look at the levels to see whether it should be included on the list.

DR. HATSUKAMI: So David, what you're saying -- I guess I would tend to agree with that -- is that we really do need a good presentation on what kind of criteria have been used for identifying some of these other toxicants. And unless we have that, then we really can't go about identifying whether a constituent should be on the list or not.

DR. BURNS: Otherwise, I think what we're doing by merging the lists is simply, basically, adopting Dietrich Hoffmann's wisdom from a decade or more ago, which is -- Dietrich is one of my favorite people, and certainly his wisdom has stood the test of time. I'm not disparaging it in any way. I'm just saying that I would think the FDA's going to need something somewhat more substantive, then we know that Dietrich was correct.

DR. HATSUKAMI: Yes. So is that something, Corinne, that the FDA can do, maybe, during the next meeting, is to present these criteria so that we can proceed on to identify the constituents?

DR. HUSTEN: Yes. And in fact, folks are working on the carcinogenic criteria, the different groups, to bring back this afternoon. So we'll see how much we can get for this meeting, even.

DR. HATSUKAMI: Great. Now, this is the list. Right? We were just passed the list that Steve had.

DR. BURNS: And I believe, in the back of the WHO monograph, for some of the compounds, Dybing and I forget the other gentleman's name had -- no, no, no, no, they did it specifically for the monograph -- have gone back through and identified the studies on inflammation and irritation, et cetera, for the non-carcinogenic compounds that are on the WHO list. So we might be able to look at the criteria that were used there to see whether their criteria we want to think about.

DR. HATSUKAMI: That's a good point.

DR. BURNS: And I think everybody was sent that -- well, I'm not sure that they were.

DR. HECHT: It's on the CD.

DR. BURNS: It's on the CD. It's at the back of the CD if people want to look at it. And there's only -- there's probably about half a dozen of the irritant compounds, acrolein and -- but acrolein's on here, so we don't need to look at it. But there's a couple of others that are on there as primary irritants.

DR. HATSUKAMI: Yes. I think that what I'd like to do is reserve the discussion for the toxicants until we really do have a handle on what kind of criteria people have used to select those toxicants.

What I would like to do is go back to the list of carcinogen constituents. And in front of you is a list that Dr. Hecht has developed. And some of them have been identified by us, but then there's additional ones that have not been.

So, Dr. Hecht, do you want to go for the ones that haven't been -- that we have not identified, and we can decide whether they should be considered for the list of harmful constituents or potentially harmful --

DR. HECHT: So under the polycyclic aromatic hydrocarbons, the IARC recent volume had evaluated a number of additional hydrocarbons to the ones that are on the original list. Furthermore, I don't know whether any of the hydrocarbons other than benzpyrene are on your list. I think I only saw benzpyrene.

So I feel that at least some, if not all, of these hydrocarbons should be on the list. I think that just using benzpyrene can become misleading. Benzpyrene has been chosen as a surrogate for other polycyclic aromatic hydrocarbons, and there is a relationship between the amount of benzpyrene in a cigarette and the amount of other polycyclics.

But benzpyrene has kind of assumed a life of its own, and I think the other polycyclics have been forgotten about. And benzpyrene levels have continually decreased in cigarette smoke, which is a good thing, and eventually they may become very low.

Then people forget about the other polycyclic hydrocarbons. I think Rodgman listed over 500 of them. I think, ultimately, the result would be that people will say, well, there's only one nanogram of benzpyrene per cigarette, so how important could that be? Well, how about the other 499 polycyclics?

So I think it's important to include polycyclics other than benzpyrene so that people don't forget that the polycyclics as a class will have different members with different carcinogenic activities and are complex in themselves.

But there's good evidence in the literature, and some of it from the older literature, that polycyclics in cigarette smoke are very important in lung cancer induction. There's plenty of evidence. So I think that, to conclude my little speech, I think we need to include some of the other compounds other than benzpyrene.

So I think that on this list -- this includes ths IARC list from Volume 83, and also the update from the recently published -- I think it's Volume 92 -- monograph on polycyclics.

DR. HATSUKAMI: So, Steve, you're proposing to include all the polycyclics?

DR. HECHT: Yes. All of them.

DR. HATSUKAMI: Dr. Burns?

DR. BURNS: I've never being reluctant to display my ignorance. I'll ask Steve and Cliff, are we better off trying to measure the individual polycyclics as individual compounds, or is it possible or preferable to measure them as a mixture, as we've talked about doing with tar?

This is beyond my depth. I don't have any idea whatsoever. But I wanted to raise that a question to see what you guys thought.

DR. HECHT: I mean, I think it would be more satisfying and more current to measure them individually, perhaps not all of them, but certainly a subset. Before, when I mentioned tar, I was thinking of, again, some of the older work on fractionation of cigarette smoke condensate and the activities of the various fractions, which a lot of people have forgotten about.

The sub-fraction that contains the polycyclic aromatic hydrocarbons has almost all the tumor-initiating activity on mouse skin of cigarette smoke condensate of tar. And there's also considerable co-carcinogenic activity and tumor-promoting activity in the weakly acidic fraction. And when you put these fractions together, you recover a lot of the activity of the whole condensate. And a lot of this has been forgotten.

So just to pick up on your comment, one thing we might consider would be trying to list the amounts of certain sub-fractions. It's never been done, and it's not too pretty, in a way, but we don't really know -- for example, we don't know what it is in the weakly acidic fraction that has tumor-promoting activity, but we do know there's tumor-promoting activity in the weakly acidic fraction.

So one might consider, in the absence of not knowing what those constituents are, to list the fraction. Just an idea. But, I mean, that gets back to the polycyclic aromatic hydrocarbon thing. In that case, we have a lot of information on individual constituents, and I think we should select a number of these, if not all of them, for the list.

DR. HATSUKAMI: Dr. Farone?

DR. FARONE: I'd just like to make a comment about Steve's idea there. We aren't at this point, as a matter of process, looking at methodology. But I'm just going to use an example of where you do a GC mass spec of a certain fraction to measure benzo[a]pyrene.

As part of that, you get out a certain number of these, you know, in the same scan or closely related, i.e., that we might want to save some of these as to which ones to remove for a methodology discussion because if it falls out of something that's easily and routinely done, then there's no reason, really, to exclude it, if it's there at a reasonably significant amount. And this list that Steve has presented has ranges in it so that you can just look at it and see that some of them are present in higher levels. We don't know whether those are the more carcinogenic.

But I think if we just stick with the idea of getting the ones on the list, when we talk about methodologies, how easy it is to do, we could come back to this question of whether you group them together and measure a fraction, or whether, just because of methodology, it's easy enough to get them individually.

DR. HATSUKAMI: That's a good point.

Cliff?

DR. WATSON: Going back to the question about benzo[a]pyrene and looking at the PHs, I mean, as pointed out, there are quite a few of these or these are substituted, halogenated, and have other substituents substituted on them. And benzo[a]pyrene has been well studied, and I think in part because it's fairly easy to analyze. Some of these other ones, particularly as you get to the high molecular weight ones, become more and more analytically challenging to measure.

My recollection is that, generally, these compounds are more or less amenable to analysis based on molecular weight or increasing chemical complexity. And so one strategy might be to pick one PH that represents the low molecular weight ones, benzo[a]pyrene, which would be sort of the middle molecular weight ones, and then 5-methylchrysene or something like that for the high molecular weight ones.

That might be another approach, grouping them together just as -- sort of like people sometimes do with the cresols because it's hard to separate some of the isomers. That's a possibility. I never really thought of that.

The other point to inject here is that the PH profile you get depends a little bit on the tobacco blend. The bright and burley tobaccos have different sorts of PH profiles. And so that was one of the reasons why I was bringing up earlier BAP as a marker because it does vary a little bit with the tobacco blend. And as we've heard this morning, that it is an agricultural process.

I'm not aware of something -- this is not my area of expertise -- but the growing practices could influence the PH distribution as well. So I think having more than one PH on the list might be a good idea.

DR. HATSUKAMI: Dr. Heck?

DR. HECK: I think that Dr. Hecht's example of the PAH class is a useful one because, we might recall from our risk assessment colleagues, that --

let's take the case of benzo[a]pyrene, which is, I guess, everyone's textbook polycyclic carcinogen.

Benzo[a]pyrene was really elevated to the confirmed human carcinogen status ranking in various agencies in fairly recent years, even though we have 50-plus years of research on it academically, and the reason being the freestanding evidence for benzo[a]pyrene as a carcinogen in humans is actually quite scant because typical exposures, heavy exposures, of persons industrially to coke oven emissions or roofing tar workers, whatever, invariably occurs as a complex array of polycyclics not unlike the one we see here in cigarette smoke.

For that reason, I'm not intimately familiar with all of these listings here, but I bet you there is scant carcinogenesis data for one or the other or many of these. But as a class, they're indicted, I think reasonably so, as a category of concern.

I think that we have available to us analytically a method for, let's say, a class example, benzo[a]pyrene. In the case of biomarkers, we have hydroxypyrene in the urine of smokers. Pyrene itself is not a carcinogen, but it's a useful index marker for this combined exposure that we may never understand the details of.

For the purposes of this listing, perhaps our ultimate purpose would be better served by taking a representative example or two or three and not necessarily concern ourselves with listing PH known to science that may or may not be in smoke.

DR. HECHT: This is not every -- these are all 2B or 2A. Okay? So there's solid evidence for carcinogenicity of all of these.

DR. HATSUKAMI: Dr. Burns, your microphone is on. Did you want to make a comment?

DR. BURNS: Reluctant as I am to pass up the opportunity to talk, I have nothing to say.

[Laughter.]

DR. HATSUKAMI: All right. So we have two opposing opinions here. One is to include all the polycyclic aromatic hydrocarbons, and then we have another set of -- another opinion, which we are selective in terms of selecting -- more selective in selecting a representative sample of the PAHs.

So is there any resolution to this issue? Yes?

DR. FARONE: There was sort of a third. I was saying include them all, but wait until we discuss methodology to determine which ones we throw off the list because I think that walks the line between the two points of view.

DR. HATSUKAMI: Yes. Thank you.

So any objections to that approach, which I favor as well? So maybe what we should do is include all of these constituents, and when we go into the topic of whether we have methods to assess these constituents, then we can decide which ones should remain on the list. Great. Good.

DR. BURNS: And we probably should keep the concept of representative for the different molecular sizes in there because that may be combined with what Bill has suggested about what falls out automatically as something we want to consider.

DR. HATSUKAMI: Good point. Yes, that sounds good.

All right. Do you want to proceed,

Dr. Hecht?

DR. HECHT: Other hydrocarbons, I think butadiene is up there. I don't know about isoprene.

Did you have isoprene?

DR. HATSUKAMI: What was that? I'm sorry.

DR. HECHT: Isoprene.

DR. HATSUKAMI: Isoprene.

Did we have that? We didn't have it on the list before.

DR. TEMPLETON-SOMERS: Yes, we did.

DR. HATSUKAMI: Yes. We did have isoprene.

DR. HECHT: You did have isoprene. Okay. And benzene you have.

You know, ethylbenzene is very weak. That's a real borderline case.

Naphthalene, I don't know. I don't think you had.

DR. HATSUKAMI: No. We didn't have naphthalene.

DR. HECHT: So I think you should have naphthalene. And I think you should have styrene.

DR. HATSUKAMI: I think we had styrene.

DR. HECHT: Styrene you have?

DR. HATSUKAMI: So we have naphthalene, and what other constituent? Isoprene we already had, right?

DR. HECHT: Yes. So you've got those.

The nitrosamines, I think you're okay because the ones on here, the four that you don't have, are not commonly measured and are not really present to any significant extent. So I think you're okay with the nitrosamines.

The aromatic amines, I don't know. Do you have ortho-Toluidine, 2-Toluidine?

DR. HATSUKAMI: I don't think we do. I don't remember going over that.

DR. HECHT: I think you need that. And I would also include 2,6-dimethylaniline.

DR. HATSUKAMI: Any objections to that?

[No response.]

DR. HECHT: And ortho-Anisidine.

DR. HATSUKAMI: And what did you say?

DR. HECHT: Ortho-Anisidine. After 4-aminobiphenyl.

DR. HATSUKAMI: That's right.

Any objections to adding that constituent?

[No response.]

DR. HECHT: I don't think you had any of the heterocyclic aromatic amines.

DR. HATSUKAMI: No, we did not.

DR. HECHT: I think one could argue about which ones to include. This gets back to the polycyclic argument again. So I would say for the time being, just include them all.

DR. HATSUKAMI: Then we'll go back and -- yes.

DR. HECHT: Then we can go back look at the methodology. And there are a couple there, like PhIP and amino-alpha-carboline, that are present in larger amounts, are easier to measure. A lot of these others are super-trace amounts and probably only been analyzed once. So I think we can come back to that.

DR. HATSUKAMI: Any objections?

[No response.]

DR. HATSUKAMI: All right. Other heterocyclics?

DR. HECHT: Other heterocyclics? Furan. I don't think you had furan.

DR. HATSUKAMI: No.

DR. HECHT: The others get into the kind of borderline area again. There's been a lot written about dibenzacridine and dibenzcarbazole. Rodgman spends about 300 pages on this going back and forth and talking about why some of the literature is wrong. I don't think there probably -- there certainly aren't routine methods for these. But on the other hand, I don't see any reason to throw them out right now.

DR. HATSUKAMI: So include them --

DR. HECHT: So I would keep them in.

DR. HATSUKAMI: -- and then have discussion as to whether we have any --

DR. HECHT: We'll get to the -- we come back to the methods. And maybe they are borderline, but probably part of the problem is that nobody's looked recently with modern methods. I mean, some of these come from reports 35 years ago. I mean, mass spectrometry has advanced quite a bit since then.

You've got formaldehyde and acetaldehyde.

You have catechol.

DR. HATSUKAMI: Right.

DR. HECHT: I think caffeic acid's kind of a borderline case.

DR. HATSUKAMI: So don't include that.

DR. HECHT: Well, it's 2B. I'm personally not sure why, but I would say that's real borderline. Some people talk about caffeic acid as a chemo preventive agent. It's in coffee, and so I don't know. I guess we can leave out caffeic acid.

DR. HATSUKAMI: So leave that out. Leave it off.

DR. HECHT: And the nitro hydrocarbons, I think we need to include these.

DR. HATSUKAMI: Include the nitro hydrocarbons?

DR. HECHT: All three of them. Yes. Yes.

DR. HATSUKAMI: Objections?

[No response.]

DR. HECHT: Then we get to the miscellaneous group. With ethylene oxide and propylene oxide, by my reading the literature, there's not much very convincing data that they're really present. But again, it might just be a function of the methods. Otherwise, I think you need to include these.

DR. HATSUKAMI: Include all the --

DR. HECHT: All of them.

DR. HATSUKAMI: All the miscellaneous organic compounds.

Any objections?

[No response.]

DR. HATSUKAMI: All right. The metals?

DR. HECHT: Include them all.

DR. HATSUKAMI: Include all the metals. I think we have some of them already on the list.

DR. HECHT: You've got most of them.

DR. HATSUKAMI: Yes. Any objections?

DR. HECHT: So I don't know. This is pretty comprehensive, but at least it goes by a set of established criteria.

DR. HATSUKAMI: Right.

DR. HECHT: I think the question with some of these is, are they really present or are there analytical methods available? If not, can those methods be -- can they be developed?

DR. HATSUKAMI: So we have a thorough list of carcinogen constituents.

Any additional constituents that needs to be added to the carcinogens? No?

Yes, Dr. Farone?

DR. FARONE: Yes. I still have a question about why pyridine shows up on the California list. But that may come into play in other areas as either an irritant or whatever.

DR. HATSUKAMI: So maybe we should reserve that until --

DR. FARONE: Well, yes. I just don't know. I mean, it is on that list. It's on a couple of other lists. And I have not had time to go back and look at the basis for why it is on those lists.

DR. HATSUKAMI: So maybe we should put that on the question mark, pyridine.

All right. Ms. Jinot?

DR. BURNS: Pyridine is on your master list as a respiratory irritant (inaudible -- off mic). It's on your master list that you sent out to us. And it's listed with Brazil and Canada.

DR. HATSUKAMI: So maybe that would --

DR. BURNS: And it's listed under non-neoplastic respiratory effect. I don't have any specific information. I'm just reporting what's --

DR. HATSUKAMI: Dr. Farone?

DR. FARONE: Yes. And it's on the Hoffmann list, too, of course, same way as being a respiratory irritant.

DR. HECK: It's also an approved food ingredient in the United States.

DR. BURNS: Not as an inhalational agent.

DR. HATSUKAMI: All right. If there's no further comments, then I think we have our list of carcinogens. All right.

(Pause)

DR. HATSUKAMI: I think we have a break at 2:30. So what I'd like to do is proceed on to talking about the constituents for addiction. So for addiction, we do have a list of constituents already. And I guess my question is, what is the criteria by which we want to choose these constituents?

Jack?

DR. HENNINGFIELD: In parallel with the approach for carcinogens, in that case relying on IARC and other methods, I think this is another case where we do have methods for judging addictiveness. FDA has probably now the most comprehensive and detailed draft guidance that is in the final works, hopefully.

But basically, I think part of its virtue is that it doesn't break a lot of new ground. It pretty much accepts what's used globally. And so I would propose that we follow that in evaluating compounds, not reinvent the wheel.

As to the list, here it's worth keeping in mind that there are substances such as nicotine that have been directly tested, and there's a lot of data. And then there are substances like acetaldehyde that have been tested in a much more limited fashion, but may have direct addicting effects.

Then there are substances that may alter the risk of addiction by altering nicotine dosing capacity, either by altering free nicotine, by altering speed of nicotine -- and again, none of these concepts are novel to nicotine; this is pretty much the way drugs are evaluated in general.

This is a case where, with smokeless tobacco products, we get into some new considerations because in the case of the smokeless tobacco products, factors such as the cutting may alter the amount and speed of nicotine delivery. The buffering is used very specifically to alter free nicotine and speed of nicotine delivery.

Ammonia was not on the list. But ammonia compounds are compounds that could increase the risk of addiction by at least two mechanisms, one mechanism being to increase the free nicotine, and one mechanism being to make the smoke smoother and easier to inhale.

So having said all of this, I think this is an area where, perhaps for the next meeting, it might be useful to have an independent presentation, perhaps by NIDA, the National Institute on Drug Abuse. They could probably do this very quickly and look at the compounds because my description of different compounds was not meant to be a final judgment, but rather examples. I think that NIDA scientists could probably go through the list and very quickly give us a table and a presentation that would allow us to concur or disagree.

I don't mean to end discussion now, but otherwise, we haven't gone through that deliberative process.

DR. HATSUKAMI: Yes?

DR. LAUTERBACH: I think we need to be very careful in some of these concepts because there's been recent literature, and I think basically we need to go on the peer reviewed literature, not what's been said in some tobacco industry report of 40 years ago. And we also need to look at some of the quality issues and some of the recent literature that people may be basing things on.

DR. HENNINGFIELD: I agree.

DR. BURNS: To be consistent with what we've done before, I think we need a specific description of the methodology to be used that we can either agree with or disagree with. I don't believe anybody has formally gone -- with the exception of nicotine, gone through the constituents of tobacco smoke and assessed them by some set of criteria as to whether they enhance addiction or not.

But I think we need the criteria. If NIDA is going to make a presentation, the first piece of that presentation has to be the decision tree, if you will, or the criteria that they used to make a judgment that compound X is or isn't contributing to addiction.

With that, I would support Jack's idea. I'm a little concerned getting too far afield into some of the cigarette engineering aspects unless we have actual data that supports it because we don't have enough information to know with certainty all of the events that are occurring from some of the additives, for example.

But in general, I think that what Jack is proposing is a reasonable one, which is to ask an entity that has criteria, and those criteria should mesh with the existing FDA criteria for addictiveness, and then ask them to apply those to the compounds that are under consideration, perhaps things such as compounds that alter the pH and various other approaches that Jack has talked about.

DR. HATSUKAMI: Dr. Farone, and then Dr. Henningfield.

DR. FARONE: Yes. I'd like to pick up on something that Dr. Jinot said earlier about structure/activity relationships. We all know that in the drug industry, it's been for 50, 60, years, anyway, used to determine likelihoods of either activity, and in this case, potential harm.

In the case of nicotine, we have some pretty good models out there because both Philip Morris and R.J. Reynolds had very extensive analogue programs, where compounds were identified which were similar. And using that type of logic and looking at those, along with maybe the NIDA-type presentation, could allow one to look at lists with the idea of whether or not the compounds on them are reasonably expected to increase the addictiveness of the product, I mean, because doing the synergy studies and all that is very difficult, as we found out with acetaldehyde. But there are some studies that have been done on analogues that are part of the literature. So that may be helpful to determining which things on the list of the 7,000; knock it down to like 10 or 16 or something like that.

DR. HATSUKAMI: Dr. Henningfield?

DR. HENNINGFIELD: To just add, in terms of the list of substances that have been thoroughly studied and known to be directly addicting, it's a very short list, most likely; maybe one. And then you probably have another category, like acetaldehyde and some of the other substances on the list; then the other category where it will be really helpful to have an outside view, which is the substances or alterations that may promote addiction.

We've come face to face with this in the menthol review in the last TPSAC meeting, and that's one of the questions that are still to be resolved, but the degree to which menthol may promote initiation and dependence, whether or not it meets criteria.

I think, rather than assuming that NIDA will get FDA input and/or input from the Drug Enforcement Administration, I think they should be encouraged to collaborate by some mechanism because FDA has its controlled substance staff and this is what they do regularly, and the same thing with the Drug Enforcement Administration. And in other areas of drugs, by law, the three agencies have input on making just that determination. So the degree to which a brief NIDA presentation follows standardized procedures, standardized criteria, I think, is really useful.

DR. HATSUKAMI: So some of the criteria that you're referring to is in the FDA guidelines, draft guidelines?

DR. HENNINGFIELD: Yes.

DR. HATSUKAMI: Do you mean the one developed by CDER?

Any other comments? Yes, Dr. Farone?

DR. FARONE: Just one thing I was thinking about as he was talking. A lot of the compounds, the degree and level to which they have, separately, CNS activity is documented and known. I mean, that's one of the general criteria that's used. And so we'd get that as part of this type of analysis. But, I mean, that's the kind of thing that I think is useful.

DR. HATSUKAMI: Was there a question, Dr. Burns?

DR. BURNS: Just a point of sort of order. May I make the request that since this list is going to go to the parent committee anyway, and the parent committee has to decide about menthol anyway, that we leave that decision to the parent committee and not have that discussion again here? Is that acceptable to the group?

DR. HATSUKAMI: Dr. Heck?

DR. HECK: And I guess I have another related observation. We haven't dealt with that a lot yet, but I did notice on the Brazil list, for instance, we have a lot of ingredients -- glycerol, ascorbic acid -- intentionally added ingredients, as opposed to tobacco and smoke constituents.

I think, given the rather extensive ingredients disclosure and judgments that are also built into other elements of the FDA regulatory authority, I think this committee, this subcommittee's, purpose would be well-served maybe to let those ingredients issues be developed and resolved and, indeed, safety judgments made by that ingredients process as opposed to weaving ingredients into this process here. We have really all we can do to try to get the narrow assignment of tobacco and smoke constituents.

I do see in the charge that, yes, the effect of ingredients on constituents is indeed part of it. But I would tend to suggest that we try to leave that as a kind of second-tier priority and get to the main task of trying to deal with the intrinsic tobacco and smoke constituents.

DR. HATSUKAMI: Corinne?

DR. HUSTEN: I just wanted to point out that the statute talks about harmful and potentially harmful constituents in tobacco products or tobacco smoke.

DR. HATSUKAMI: All right. Dr. Farone?

DR. FARONE: Yes. I'd like to also point out that once you put the material on the tobacco and you burn it, it's part of the smoke. So I don't see how you can not take into account what you put onto the tobacco.

I mean, if it was 20 percent sugar and you're looking for acetaldehyde, that's where a lot of it's going to come from. So I think that it's taken care of in looking for the chemicals that are derived from it. Somebody mentioned before whether it's chocolate that you're putting on there, well, okay, chocolate has theobromine in it. I don't know that there's any theobromine in tobacco. If you detected theobromine in tobacco smoke, where would it come from? So there is this connection between the whole product and what you put on it that I don't think we can ignore.

DR. HECK: Point taken. But I think that just trying to minimize the duplication effort between different subsets of this committee and different activities going in parallel, that we don't want to duplicate other efforts that may be underway or anticipated in terms of the ingredients issue separately.

DR. HATSUKAMI: Any other comments on that particular topic?

[No response.]

DR. HATSUKAMI: So if not, I think we're going to take a break. What I'm hearing is that for the next meeting, we need presentations both for the non-cancer constituents and the addiction. We need presentations in terms of what are some of the criteria that can be used to select these constituents.

DR. HUSTEN: If you could clarify around -- I understood the NIDA presentation. I'm not sure I had heard about another presentation. So if you can clarify around which specific -- who and on what, that would be helpful.

DR. HATSUKAMI: David, do you want to take that on?

DR. BURNS: Well, I don't have a who. But the issue is that EPA and others have made assessments of the respiratory and cardiovascular effects of air pollution and a variety of other things. They almost certainly have methodologies by which they make the assessment that a specific compound creates a specific problem.

It would be very useful to know what that methodology is as we approach the question of trying to apply what I would expect to be a similar or identical methodology to the data on tobacco. And certainly, if they've done that for some of the constituents on tobacco, it would be very helpful to have that information presented as well.

DR. HUSTEN: And perhaps Jennifer could address a little bit the criteria. And actually, she had given me a website where it lists which ones have met their criteria, and we are trying to get that information for you.

DR. HATSUKAMI: And we're going to be focusing mostly on the respiratory and the cardiovascular disease.

Is that right?

DR. BURNS: That was my understanding of the charge we were given. The others are even more complicated if you're going to deal with complications of pregnancy or, for that matter, teratogenicity. I'd say teratogenicity methodology is fairly well worked out. I'm not sure that we have much evidence on it, is all.

MS. JINOT: Yes. I can just briefly now address what EPA does. We've got specific guidelines for reproductive and developmental toxicity, for example. I don't believe we do for respiratory effects or cardiovascular. But when we come across effects in the literature for the chemicals that we're examining, we do evaluate them for if there's sufficient evidence for an adverse toxicity. And if it's respiratory, then we would take that into account in the assessment.

Then the assessments are externally peer-reviewed. So what's in the assessments that are on the Integrated Risk Information System, or the IRIS database for EPA, even if we don't have specific guidelines, they've been evaluated for toxicity and then been externally peer-reviewed. So maybe the database in and of itself could be considered a criteria that we could accept.

DR. BURNS: In doing that evaluation, they certainly must express some criteria by which they arrived at that judgment.

MS. JINOT: Well, in individual assessment they might, or what level of -- why they would say that evidence of an irritant effect was considered adequate and sufficient. But we don't have guidelines for that, general guidelines, what IARC has for carcinogens, for what we do.

DR. BURNS: But there ought to be some kind of commonality across them that -- there's some kind of commonality across them that would at least be useful to us in considering what we're doing here.

MS. JINOT: Right. That could be.

DR. HECHT: Or on a case-by-case basis.

DR. BURNS: Well, the problem with going on a case-by-case basis is we're going to have to review the entire world literature on each individual compound here is a group in order to reach --

DR. HECHT: Well, it's been reviewed by EPA.

DR. BURNS: To the extent that they've been reviewed by EPA and EPA has reached a judgment, our job is much simpler. What I'm hearing, though, is they have case-by-case evaluations, and that may not include all of the compounds that we're concerned with. If they do, then I'm all for not recreating any kind of second review process when it's already been done.

But the question is what we have already. And we're asking for some presentation on what we have already so that we can then move from that point on. We're not interested in second-guessing the process in any way other than understanding it.

MS. JINOT: Right. I think for respiratory effects, the things that are typically looked for are the irritant effects, and also decrements in respiratory function. And those would be standardly measured parameters.

For the cardiovascular, that's not something that's typically addressed in toxicity assays. I mean, there are some specific things, like carbon monoxide, but that is more case-by-case. So I think that one might be a little harder to have standard methods for.

DR. HATSUKAMI: Dr. Farone?

DR. FARONE: Yes. I think the question to what level we consider developmental, or teratogenic, if you will, but developmental effects, both EPA and I know the California list has a whole separate section with criteria developed for chemicals that cause developmental harm.

The good news is that a lot of those chemicals we've already talked about because they appear on both lists. The bad news is that there are some chemicals that are specific to smoke that aren't on the carcinogenicity list that are on the developmental list there. And I don't really know where that fits into our charge.

DR. HATSUKAMI: Dr. Husten?

DR. HUSTEN: You are free to use the criteria that you think are important. We were just trying to give you some summary data to get the discussion started.

I guess my question about the ISIS list is whether -- IRIS, sorry, IRIS list. I know you can go in and search on specific compounds, but is there a way to download by category? Because we'd have to figure out how you reconcile the two lists. I think we can take the lists that we're starting with and look them up in IRIS fairly easily.

DR. HATSUKAMI: Dr. Farone?

DR. FARONE: Yes. Maybe the suggestion might be where there is -- on a chemical, we're going to have a list. Where there is a developmental component of that, we could list it, because for many of them it is known. And maybe then where there are some chemicals that represent some large developmental harm -- that is, at very small levels, they've been shown to be active -- then we might consider adding those to the list of something that should be put on the major list.

DR. HATSUKAMI: All right. So what I'm hearing is that we should consider some of the reproductive --

Any other comments before we take a break?

[No response.]

DR. HATSUKAMI: I think we're going to go ahead and take our break. And we'll reconvene at 2:45, so we have some period of time.

Again, I want to remind the committee members and consultants that there will be no discussion of the meeting topic during the break amongst yourselves or with members of the audience. And anybody that is in the public hearing, if you could please sign in, we'd appreciate it. Thank you.

(Whereupon, a recess was taken.)

DR. HATSUKAMI: I think we're going to get started. So if you can have your seats.

Just to let people know what we're going to do for the rest of the day, we're going to have the open public hearing right now. And then after that, we are going to have Dr. Cliff Watson present his lecture on methods. And then for tomorrow, we'll reserve any additional information that the FDA wants to present to us, and then we'll be going back to our list.

So prior to the open public hearing, I need to make a few statements.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with a sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of this issue before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

So the first speakers to present are Ryan Lanier and Curtis Wright from Rock Creek Pharmaceuticals, Incorporated/Star Scientific.

DR. LANIER: Thank you. I'd like to begin by thanking the committee for the opportunity to speak here today. I am Ryan Lanier. This is Dr. Curtis Wright. We do work for Rock Creek Pharmaceuticals, Incorporated, which is a wholly-owned subsidiary of Star Scientific, which makes tobacco products. And we're here today to present to you Star's recommendations for measurement of toxic tobacco constituents.

So as we have already heard today, there are thousands of chemical constituents in tobacco and in tobacco smoke. However, when choosing tobacco constituents for measurement, there must be certain criteria that are met. These criteria include the constituent must be known to be present in toxic amounts; there must be evidence it can be controlled; and the anticipated benefits must be substantial.

The constituents that Star recommends as candidates include NNK and NNN, which we've heard about previously today; these are two tobacco-specific nitrosamines that are known to have carcinogenic activity; the total tobacco-specific nitrosamines, which are NNN, NNK, NAT, plus NAB; and benzo[a]pyrene, both as a primary carcinogen and as a marker of carcinogenic polycyclic aromatic hydrocarbon content.

So now I'll briefly describe each of these in just a bit more detail.

First are NNK and NNN. Again, these are two tobacco-specific nitrosamines. There's a wealth of literature showing that these are carcinogenic in animals. Two recent studies have also linked levels of the metabolite NNAL, which is an NNK metabolite, to cancer in humans. And these two TSNAs are both group 1 carcinogens according to the IARC. They're found in both tobacco and smoke condensate, and there are very broad ranges found in both smoked and smokeless products.

Also, there is very strong evidence levels of these can be controlled, and standard and living methods are already available. And these TSNAs can be expressed both per unit of tobacco as well as per milligram of nicotine.

This figure shows the type of variability we've seen with NNK and NNN. These data are from a study performed by Gray, et al. in 2000. They tested three global brands of cigarettes in 21 different countries. This figure came from that paper. This shows NNK levels expressed as nanograms per cigarette. And what they found was a ninefold variation in NNK levels within one brand, within Marlboros, between those tested in Mexico and the United States, again emphasizing that levels of these TSNAs can be controlled.

In addition, even though this paper was published 10 years ago, a more recent paper just published in the last few weeks from scientists at the

CDC have shown very similar results, with NNK and NNN levels being quite high from smokers in the U.S. as compared to other countries, such as Australia and Canada.

Next are total TSNAs. This would be one number that consists of the summation of NNN, NNK, NAT, and NAB. There's again very strong evidence suggesting that total TSNA levels are linked with cancer. There are broad ranges of TSNAs found in smoked and smokeless products. Again, strong analytical methods are currently available to test for TSNAs. And TSNAs may be expressed both per unit of tobacco as well as per milligram of nicotine. Also, giving a total TSNA level or value resolves the problem of how to handle NAT and NAB, which we have already heard today, there is limited evidence that these have carcinogenic activity.

This figure shows us the TSNA variability that is found among different types of smokeless products. These data are expressed as total TSNAs expressed as nanograms per gram or parts per billion. And what has been found is that in older smokeless products, such as historic dry snuffs, TSNA levels can be very high, approaching 100,000 nanograms per gram, whereas more modern products, including low-TSNA products, have levels that are only in the 1- to 200 parts per billion range.

Next is benzo[a]pyrene, or BaP. Soot has been known to be carcinogenic for centuries. This was first demonstrated by Sir Percivall Pott in the 1700s, when he linked scrotal carcinoma in chimney sweeps to their exposure to soot. Soot has a number of different polycyclic aromatic hydrocarbons within it, and BaP is the paradigmatic (phonetic) carcinogenic hydrocarbon.

It's found in both tobacco and smoke condensate. Again, a broad range is found in smoked and smokeless tobacco products, and strong evidence exists that levels can be controlled. Standard analytic methods are currently available for measuring BaP. And again, much like the TSNAs, BaP levels can be expressed both per unit and per milligram of nicotine.

This figure shows BaP variability found

among a number of different types of tobacco products. This is BaP levels expressed as nanograms per gram, or parts per billion, for all products listed except for cigarettes on here. Cigarettes are actually listed or actually expressed per unit or per cigarette.

What this figure shows us is that in certain oral tobacco products, such as Copenhagen and Skoal, which are moist snuffs and are very popular in the U.S., BaP levels may be very high; whereas on the right side, with more modern products, such as dissolvable products in Marlboro Snus, BaP levels can be quite low; actually, in this instance, lower than those found in grilled meat. And again, in cigarettes, there is also BaP variability depending often on the yield, the type of yield, whether it's high or low yield.

So measurement and reporting of toxins in a commercial product should be designed to lead to positive health outcomes -- that's the purpose -- and should avoid risk of distortion through advertising. Trace contaminants like TSNAs and BaP should be reported both per unit of use, such as cigarette, lozenge, pinch, et cetera, as well as per milligram of nicotine, since nicotine is the primary psychoactive component in tobacco. This is similar to foods labeling, which reports both quantity data, or calories per serving, and percent of normal diet data to the consumer.

This figure shows BaP, NNN, and NNK when expressed per cigarette relative to tar and nicotine yield. And what this figure shows us is that if all things were held equal and smokers smoking very low and low yield cigarettes smoked them the same way as high and very high yield cigarettes, they would actually benefit from smoking these lower yield cigarettes because the amount of toxins they would consume would also be lower. However, what this does not take into account is compensation, in which smokers alter the way they smoke by smoking more intensely or smoking more frequently or smoking more cigarettes.

When these same toxins are expressed per milligram of nicotine and by taking into account compensation, we see that smokers smoking very low and low yield cigarettes may actually increase the levels of these toxins that they consume along with the nicotine.

So for these reasons, this variation in nicotine content among products as well as the nicotine delivered from different products, Star believes it is very important to express levels of toxins both per portion of tobacco as well as per milligram of nicotine.

This is a tobacco label that we propose. It looks much like a food label. It's meant to be easy to understand and easy to read. This would be for a smokeless tobacco product. It shows the portion size, the portions per package, clearly labels the amount of nicotine per portion, and then, in the section below, lists total TSNAs, NNK, NNN, and BaP, showing both per portion and per milligram nicotine content.

Now, although parts per billion may not be familiar to many consumers, if all tobacco products were labeled in such a way, it would be very easy for consumers to make side-by-side comparisons, and be easier for them, if they wanted to, to choose products that actually contain fewer amounts of toxins, especially relative to the amount of nicotine that they're consuming.

So in conclusion, we recommend as harmful constituents the two tobacco-specific nitrosamines that are known to be carcinogenic, NNK and NNN; total tobacco-specific nitrosamines, which would be a summation of NNN, NNK, NAT, and NAB; and benzo[a]pyrene, both as a primary carcinogen as well as an indicator of polycyclic aromatic hydrocarbon content. Thank you.

DR. HATSUKAMI: Dr. Wright, you have about a couple minutes to speak.

DR. WRIGHT: I only have one thing to say.

DR. HATSUKAMI: Good.

DR. WRIGHT: You're putting together a list, and I think that that is an admirable activity, and it's also mandated by law. But I think the real question comes down to whether you will in fact grant the wish of one of our past surgeon generals, that tobacco products be fairly labeled with their toxin content so that those who use them will know what risks they face. That is where this is all coming to.

There is also a suggestion made in that same statement that products should be made by reducing the avoidable risk associated with the products to a minimum. So to the question that was raised earlier today, yes; if a carcinogen is in a tobacco product and it may be practically removed, it should be. Thank you.

DR. HATSUKAMI: Does the committee have any questions for the speakers?

[No response.]

DR. HATSUKAMI: No? Then we'll go ahead and proceed on to the next speaker, Ronald Tully from National Tobacco Company.

MR. TULLY: I'm Ron Tully, National Tobacco Company. I'm a vice president with the company. I also work with the Council of Independent Tobacco Manufacturers of America, CITMA. And I was pleased that Dr. Johnson was able to outline some of the issues that face small manufacturers to some extent. I'm going to review some of those issues again. And I know there's little interest in the committee in terms of the economic impact of some of these testing burdens that may come out of the compilation of this list, but I think it's important for the public record that they're understood.

But I would like to clarify a couple of things that came up this morning relative to what Dr. Johnson had to say, and that is, firstly, small companies are willing to test our products. We are willing, and in fact, many of the small companies who are members of CITMA actively supported the passage of the legislation, and worked with members of Congress in defining the role of small manufacturers and their obligations within the context of this legislation. So we recognize our obligation, and we recognize our need for compliance with the regulations on product testing.

The problem for small companies is that if we end up with a list of 8,000 chemical compounds that need to be tested, either in smoke or tobacco products, we face the prospect of going out of business. And that may not be an issue of concern to the committee as such, but it is an issue of concern to the many people who are involved in manufacturing small tobacco manufactured products, and also vital and important relative to maintaining a competitive and healthy tobacco sector. And I use the word "healthy" not in the sense of -- I mean competitively healthy.

Oh, sorry. I thought I had some slides up there. It's okay. It doesn't matter. I'll work from here.

I'd just like to reiterate a couple of things that Dr. Johnson said this morning. Firstly, small tobacco is not big tobacco. And I think it's very easy to view the industry in broad terms, but we are different in terms of the way in which we manufacture our products; we are different in terms of the way in which we source our products; and we are different in the terms of the way in which we market our products to consumers. And much of our marketing is directed at the point of sale and not directly at the consumer himself. So we're really competing in the marketplace from the point at which the product is purchased rather than at a broader base mass communication level.

We make what we would consider to be conventional and traditional tobacco products. We buy components, we buy filters, we buy papers, we buy tobacco. Sometimes we don't know where that tobacco comes from. And often that tobacco is sourced and blended for us by a third party.

Clearly, within the framework of FDA regulation, we need to better understand the control points in our product from a good manufacturing practice perspective. And we anticipate that we will be doing that at some point as FDA mandates regulation in that area.

So we recognize our responsibility. We recognize there's a need for us to do as much as we can in terms of being responsive to the needs of both the agency, in terms of the rulemaking it sets for us, and be responsive to the needs of consumers in terms of what the agency mandates we provide by way of information to consumers.

It is important that we maintain a competitive marketplace. It's interesting. Star was up here a few moments ago, and they talk very well about the innovations that they have created in the marketplace, and they have a structure as a small business that's been based on a harm reduction strategy for their products. They're a tiny business. They're doing something different in the tobacco industry. And to some extent, it's small companies like Star that actually help change the paradigm and move the debate slightly further forward than the debate we've had over the last 50 years relative to tobacco.

So maintaining small companies in the marketplace is important from that sort of perspective. But let's be realistic. Let's be realistic about what small companies can do. We have very limited -- on the whole, very limited scientific capability in-house. Very little access to the sort of scientific structures that are available within large tobacco companies. And we essentially rely on third parties to tell us what's in our product, both from the supply side and what's in our product on the testing side. That's the reality of where we are today.

If we move forward with a very, very comprehensive list, the reality for us tomorrow is that we'll be out of business within a very short period of time because the testing obligations may be so onerous on us that it just does not allow us to maintain a presence in the marketplace.

If the objective of producing a list is to allow two large competitors to survive in the marketplace, then that's not a legitimate purpose for creating the list. From our perspective, the list must be based on certain key criteria. Firstly, that the comprehensive listing should be based on final testing of the product, on the final manufactured product and not on the components of the fabricated product. Consumers are not consuming the components. They are consuming the final product.

It may be appropriate to test tobacco in its unburned state, but it may also be appropriate to test the final product in its finished state. But all the intervening stages are really irrelevant in terms of how the consumer consumes the product.

So you may need a baseline of testing on things like metals, heavy metals in the tobacco in its unburned state, and you may need a reference point in terms of that type of testing of the product in its finished state. But we don't need all the components tested along the way. So we have some concerns that members of the committee may take a view that test, test, test, all the way through to an extent that it's impossible for businesses to actually manage that process.

So what we recommend to the committee, particularly, that we involve the Office to Assist Small Tobacco Product Manufacturers, which is an entity which should have been established within the agency relatively quickly as a statutory obligation, and yet has to be created within the agency, to act as a reference, a technical reference point, through which small manufacturers can help increase awareness relative to small manufacturer issues, and also provide a forum on the issue relative to constituents that impacts small business.

That office is very important to the small manufacturers. It was a negotiated term, a provision within the legislation, and the agency has done nothing to date to establish the support mechanism that small manufacturers need in order to survive.

So it's sort of illustrative to us, and of concern to us, that the agency's not concerned with -- it's only concerned with the burdens -- it's only concerned with placing burdens on manufacturers and not facilitating the process of communication with small manufacturers, and I think that issue has to be addressed as soon as possible.

I think we should base the listing of harmful constituents on sound, peer-reviewed science, and it's encouraging to hear the debate of the committee that's gone on today relative to that issue, and based on threshold limits established by primary U.S. sources, such as the Environmental Protection Agency, OSHA, and other federal agencies.

We have no problem with attempting to manufacture products within certain tolerances and meeting those requirements and obligations. But you can't produce a list of 8,000 tolerances and ask us to meet all of those and test to all of those. It's impossible for small business to do.

Also, any inclusion of any compound within the constituents list should be based on the Federal Data Quality Act. And we believe, as Star has pointed out, that making any list of harmful constituents available actually is based on the purpose of communicating something to consumers about the product to increase consumer understanding about what it is they are consuming.

Thank you very much.

DR. HATSUKAMI: Thank you, Mr. Tully.

Any questions from the committee?

[No response.]

DR. HATSUKAMI: No? Thank you.

Our next speaker is Mark Haney from Kentucky Farm Bureau.

MR. HANEY: Good afternoon. Thank you very much. My name is Mark Haney. I'm president of Kentucky Farm Bureau, Kentucky's largest farm organization in our state, with more than 483,000 family members. But more importantly today, I'm speaking on behalf of our more than 6,000 growers, family growers that produce in our state, in Kentucky. I'm here speaking on behalf of no one other than our membership.

Tobacco continues to be a major part of the farm economy in Kentucky. Tobacco production not only impacts the livelihood of those farm families raising the crop, but it also impacts thousands of workers across the state.

Tobacco production in Kentucky has fallen from the over a billion dollar level of the mid-'80s to more than $300 million in today's current farm receipts. It is grown in most all of 120 counties that we have in Kentucky.

Kentucky primarily produces three types of tobacco, burley, dark air-cured tobacco, and dark fire-cured tobacco, and it's the nation's largest producers of each of those varieties.

Burley tobacco is a light, air-cured type tobacco used primarily for cigarette blends. Dark air-cured tobacco is used primarily for chewing and cigar products. And dark fire-cured tobacco is almost exclusively used in smokeless tobacco products.

It's our policy that farmers follow good agricultural practices that are practical, legally approved, and based on sound science. And we ask the same of any regulatory oversight, that it be based on sound science, and that any changes required in the industry, and ultimately for our farmers at the farm level, be practical and not mandate modifications to components that naturally occur in the tobacco leaf.

Today, in an effort to reduce TSNA accumulation in the leaf, tobacco farmers utilize tobacco seed of low converter varieties. And I want to say that the University of Kentucky is doing a very active and very successful plant-breeding project that's now underway that will soon result in varieties that will have much lower nornicotine conversion than current varieties.

Likewise, today's producers routinely test its production field soil fertility and applies only those crop nutrients necessary for efficient production. Nitrogen fertilizer use, another factor that influences TSNA levels in tobacco leaf, has been reduced.

Curing practices have also improved significantly over the years, resulting in conditions that reduce TSNA accumulation in the leaf. Kentucky farmers have been quick to utilize proven production practices in proactive ways to reduce levels of harmful constituents in the tobacco leaf.

Basic production practices are similar for each of the three types of tobacco that we grow in Kentucky, but due to the fact that weather conditions and curing practices can play a large role in TSNA accumulation, growers continue to focus on various cultural practices to minimize accrual.

Producers manage their crop utilizing good agricultural practices for efficient production, harvesting, and curing of tobacco. Many tobacco producers have added newer curing barns that allow for more control in the curing process.

While there is little a grower can do to control ambient temperature and humidity, managed ventilation is a key so that there is an adequate balance of enough humidity for good quality and enough ventilation to minimize the TSNA formation.

Dark-fired cured tobacco production is truly an art that has been practiced for more than 200 years in our state, and involves the introduction of heat and smoke to finish the curing process of the crop.

In years past, producers have fired their crop as many as maybe eight times or more, and this process involves the use of natural wood slabs, slowly under natural wood sawdust, to generate a curing temperature of 100 to 135 degrees inside the barn during various stages of curing in the leaf, and the introduction of wood smoke to finish the crop and give it the distinctive characteristics that the processors want.

Modern dark-fired cured producers have also adopted a number of improved practices to reduce the concentrations of various leaf constituents. For example, producers now limit the number of firings to finish their leaf in an effort to reduce any TSNA formation.

Tobacco producers are innovators, and readily adopt proven production technologies that will improve their production efficiently while raising a product that will be as safe as possible. Following good agricultural practices is paramount to producing top quality tobacco crops that have lower TSNA levels or other unfavorable characteristics.

Kentucky's tobacco producers are willing to employ new and proven practices to maintain their way of life. Tobacco production is important to the livelihood of thousands of Kentuckians, and I urge good common sense from this committee as we move forward.

Thank you for the opportunity to be here and speak on behalf of the producers of my state.

DR. HATSUKAMI: Thank you, Mr. Haney.

Any questions from the committee?

[No response.]

MR. HANEY: Thank you.

DR. HATSUKAMI: Thank you.

Our next speaker is Dr. Richard Higby from Arista Laboratories.

DR. HIGBY: Thank you, Madam Chairman and members of the committee, for the opportunity to speak to you today. I'm really speaking on the third of the committee's charge, which is acceptable analytical methods for assessing the quantity of each constituent.

Arista Laboratories is an independent and ISO 17025-accredited laboratory specializing in analysis of tobacco and tobacco products and smoke constituents. Arista's independent nature means that we do accept contracts from all parties, including tobacco manufacturers, regulators, academics, and others with an interest in high-quality analytical results.

We are a member of CORESTA, NCI's Tobacco Products Assessment Consortium, or TobRAC, ASTM, and the U.S. Technical Advisory Group to ISO Technical Committee 126. My comments today are made in my capacity as president of Arista Laboratories.

I have four key points that I'd like to make today. And those are, number one, analytical methods should not be prescribed by law; a defined quality system is necessary in testing products; three, machine smoking conditions must be clearly defined;

and four, replicate requirements need to be explicitly stated.

Speaking to the first of those, analytical methods should not be prescribed by law, methods validated through the process of collaborative study procedures are valuable reference documents to analytical laboratories and formed in many cases the basis of accreditation for the analysis of specific compounds.

Collaborative studies are conducted through a process requiring cooperation and support, typically from a minimum of 10 laboratories, conducted at great expense and over a long period of time. Results from collaborative studies are published and made generally available by standards organizations.

Relevant methods for tobacco and smoke constituents can be found from the International Organization for Standardization, or ISO, but only six methods exist today that are published for the analysis of constituents in mainstream smoke, covering a narrow range of analytes, specifically tar, nicotine, carbon monoxide, water, alkaloids, and benzo[a]pyrene.

The continued development of ISO methodology relative to cigarette products is in the interest of groups such as the Cooperation Centre for Scientific Research Relative to Tobacco, or CORESTA, and WHO's Tobacco Laboratory Network, or TobLabNet. Both groups are active in promoting methodology to ISO, but have limited productivity, given the lengthy collaborative process. The establishment of methods suitable to address all the constituents of likely interest to the FDA will require many more years, if not decades, to complete.

Other method sources from various publications, such as Health Canada's Tobacco Reporting Regulations, or TRR, the Centers for Disease Control, ASTM International, or WHO's TobReg, do not necessarily utilize a collaborative study approach to verify methodology. This presents methods from single perspectives, without the benefit of peer review.

It is not unusual for these published methods to contain conflicting detail, insufficient descriptions, or just fully erroneous information through typographical errors, that prevents a verbatim execution of the method. When such methods are codified, as in the case of Health Canada's TRR, it presents a situation whereby a laboratory may be technically forced to violate the law in order to complete the analysis.

Absent the type of data completed in a collaborative study, that is, a statistic suitable to evaluate improvements in specificity, accuracy, precision, and other metrics vital to interpreting results, data collection becomes data collection for its own sake and does not provide a framework by which product standards can be developed.

We do not favor prescriptive and codified methods that inhibit the development of new technology. Laboratories should have the freedom to improve technology, utilize state-of-art technology, and improve operational costs as available.

Accordingly, Arista Laboratories favors an approach that relies upon sound principles of validation such as those found in the International Committee on Harmonization, or the FDA's Guidance for

Industry on Bioanalytical Method Validation, and open to inspection by a third party accreditation authority such as the American Association of Laboratory Accreditation.

My second point. A defined quality system is necessary. Independent third party accreditation to an internationally accepted standard, such as ISO 17025, supports a level of competency across the range of analytical methods for the testing of tobacco products. Scheduled and periodic review of a laboratory's quality system through the accreditation process encourages an environment of continuous improvement in systems and management.

Commercial and industry laboratories presently exist that are accredited to perform the analysis of tobacco products, including smoke constituents, in conformance with ISO 17025. In many cases, the methods listed on the respective scopes of accreditation have been the subject of industry collaborative studies, reflect years of analytical expertise in the field of tobacco analysis, and are optimized, rugged, and free of interferences, all of which are requirements of an optimized method.

An alternative to accreditation is conformance to good laboratory practices consistent with the regulation of pharmaceuticals, food, and pesticides. Laboratories that have the competency to perform the analysis of tobacco products, including smoke constituents, have not typically undertaken the burden of GOP because of the advent of ISO 17025 as a superior quality management practice fit for the purpose of the analysis.

Furthermore, the industry-unique environment used for the machine smoking of tobacco products does not conform to GOP principles, and will take some time to establish. The FDA needs to understand that the demand for such equipment, such as smoking machines, is very much smaller than in other industries, such as the food, environmental, or pharmaceutical analytical testing markets, and the market demand for such equipment is declining with the consolidation of the industry and the rationalization of product lines.

Inspiring instrument manufacturers to rework their equipment to a GOP standard will come at a significant expense to a few laboratories, such as Arista, and will delay our ability to comply with the Act if under GOP.

We fully support a quality standard such as ISO 17025 and accreditation through third party, independent organizations. We do not support a GOP requirement.

My third point. Machine smoking conditions must be clearly defined. It is understood that machine smoking methods are not representative of human smoking behavior. However, cigarette smoking conditions must be uniform across laboratories for results to be comparable over time and useful in establishing a product standard and interpreting product trends.

Such conditions should include parameters such as those found in the existing ISO standards for smoking or as published in the Health Canada Tobacco Reporting Regulations, with reference to the ISO standards.

My fourth point. Replicate requirements need to be explicitly stated. Natural products, as we've heard today, are inherently variable despite mass production under seemingly uniform conditions. The variability arising from the products, combined with variability in machine smoking prior to analytical methods, makes it imperative that a sufficient number of replicate analyses are conducted to give statistical significance to the data.

The number of replicates should be clearly stated in the testing requirements and relate to the form of the product under consideration. That is, tobacco constituents may have a different number of replicates than smoke constituents. For example, it should be noted that the Health Canada TRR prescribes seven replicates for smoke analysis and three replicates for tobacco. We agree with this approach.

We encourage FDA to consider setting replicates required for all smoke constituents at this same number to facilitate laboratory optimization and allow correlation between constituents as products evolve. It's important that the statistics are comparable. This has not always been the case for the Health Canada TRR, the Massachusetts Department of

Health, or the Federal Trade Commission, where the number of replicates for tar, nicotine, or carbon monoxide is set at 20 while other analyses are at a lesser number.

Really, in conclusion, I'd like to just emphasize the timetable for reporting, as defined in the Act, is a short 12 months after the publication of the list of harmful and potentially harmful constituents. Establishing laboratory capacity for completing this work at any level is a challenge, and I'd encourage this committee and the FDA to work toward the early establishment of the list of constituents and the testing requirements specific to tobacco.

Thank you for the opportunity to speak today, and I'd be happy to answer any questions.

DR. HATSUKAMI: Thank you, Dr. Higby.

Any questions from the committee?

Yes, Dr. Lauterbach?

DR. LAUTERBACH: Dr. Higby, in very round numbers, what is it going to cost a tobacco manufacturer for unique brand style to get some of the data that the committee's talked about today, such as the original analytes list?

DR. HIGBY: It's almost an impossible question to ask -- or to answer, Dr. Lauterbach; of course you can ask it. Right now, the committee is in the process of establishing the list, and I was right with you up until about 1:45, but then it seems that we went a bit over and beyond what I could give a fair estimate on.

It is dependent upon the number of brand styles that would go through a laboratory; what kind of efficiency gains we could get; what the critical path to testing is; and, probably more importantly, what the timetable is for getting that testing completed. If we are to receive 300 brand styles on January 1st and we don't have to report results for five years, it's easy. If we have to report those results in 30 days, it's hard. It takes more resources.

So without defining some of these parameters a bit better, I'd be hesitant to give you a price value.

DR. LAUTERBACH: Well, compared with other laboratory tests that people might be familiar with, I mean, is it $100 per sample or 10,000?

DR. HIGBY: Well, you're talking about tens of thousands of dollars, I would guess, by the time this committee is done establishing the list, the smoking conditions, and the reporting requirements.

DR. HATSUKAMI: Any other questions from the committee?

[No response.]

DR. HATSUKAMI: Okay. Thank you, Dr. Higby.

Our next speaker is Dr. Kerry Lane.

DR. LANE: Good afternoon. My name's Kerry Scott Lane. It's a pleasure to speak here today in front of the FDA Tobacco Science Subcommittee.

I'm a board-certified anesthesiologist. I practice in West Palm Beach, Florida. I've had a longstanding interest in environmental toxicology, specifically fungal toxicology. I'm here today to request the Tobacco Scientific Subcommittee include aflatoxin in the list of regulated hazardous compounds that should be minimized on tobacco products. The FDA should regulate aflatoxin on tobaccos. The FDA has regulated aflatoxin on all other agricultural commodities since 1966.

The fungal carcinogen aflatoxin was first identified in 1960. It is now recognized as the most potent carcinogen known, and is prototypically used in lab experiments as a positive control, as opposed to all the other compounds we just saw today.

It causes mutations in the p53 tumor suppressor gene as well as ras mutations, which are involved in the majority of human cancers. Tobacco-related cancers, including those associated with environmental tobacco smoke, often show the same p53 mutations associated with aflatoxin exposure.

Aflatoxin is a known contaminant on flue-cured tobacco leaves and has been found in environmental tobacco smoke. That aflatoxin is found in ETS is not surprising as it is heat-stable, often surviving combustion.

Dietary exposure to aflatoxin indicates it is an hepatotoxin and liver carcinogen. Aflatoxin has a potential, in primary and secondary smoke and chewing tobacco, to be a potent carcinogen.

Aflatoxins are produced by fungi that invade agriculture commodities under warm and wet storage conditions after harvesting. Aflatoxin has been recognized as a teratogen, mutagen, carcinogen, immunosuppressant, and potent inhibitor of protein synthesis.

As I mentioned earlier, the Food and Drug Administration began regulating aflatoxin on agricultural commodities such as peanuts, corn, and grains in 1966. International, federal, and state laws prohibit interstate shipment of contaminated aflatoxin commodities exceeding 20 parts per billion, while the level for milk is one-half part per billion.

Ignorance with respect to level of tobacco contamination by aflatoxin, and lack of a clear FDA rule, has resulted in a public health catastrophe. Contamination of aflatoxin may occur during extended storage time as well as during the curing process, yet there is little agricultural literature on this subject.

Researchers at the United States Department of Agriculture examined, "Fungi isolated from flue-cured tobacco at time of sale and after storage" in 1969 and found most of the species regularly found on tobacco are capable of aflatoxin or other dangerous mycotoxin production. That same year, Harold Pattee of the United States Department of Agriculture found, "Under favorable growth conditions, aspergillus flavus can produce aflatoxin on flue-cured tobacco leaves."

Aflatoxin is 200 times more carcinogenic than benzpyrene, and decomposes at 516 degrees Fahrenheit, well above the combustion temperature of an idling cigarette. In 1968, researchers found a 100 percent carryover of aflatoxin from combusted tobacco. The heat stability of aflatoxin may explain the toxicity of environmental tobacco smoke. Use of smokeless tobacco products often leads to oral cancers after several years. Uncombusted aflatoxin may be a causal agent or promoter of the early onset of oral malignancies, as p53 mutations have been found in tumors in proximity to the oral cavity.

Aflatoxin has been shown to cause cancer in every animal model and cellular system studied, and to form adducts in the p53 tumor suppressor gene that mutates in approximately half of all cancers. Additionally, aflatoxin adducts to DNA and binds to glutathione, causing cancer-like states. Aflatoxin is a pulmonary carcinogen in experimental animals, and has been found in lung cancer tumor tissue. Epidemiological studies have shown an association between aflatoxin exposure in farmers and their subsequent lung cancer.

The evidence I have cited is a compelling reason for the FDA to regulate aflatoxin levels on tobacco. The FDA and international bodies already regulate aflatoxin on all other agricultural commodities. The technology to prevent, remediate, and terminally test for these toxins is currently available for a fraction of the cost of the morbidity and mortality it will prevent.

Financial disclosure, I own three United States and worldwide patents that are respective toward solving this aflatoxin/tobacco problem. And I have several minutes left. I'd just like to speak about the p53 mutations which aflatoxins have been shown to cause. It also appears that nitrosamines can cause p53 mutations. These are lung cancer mutational spectras; you can't really see it, but most of these show a high correlation with p53 cancer and environmental tobacco smoke, which may be related to aflatoxin exposure.

Breast cancer p53 mutations. As I said, aflatoxin is a carcinogen, teratogen, mutagen. It's immunosuppressive. It's likely aflatoxin is causing immunosuppression and making the AIDS epidemic worse.

While we're on the subject of fungal toxins, there are two other toxins that I'll mention off the top of my head. This whole process of curing tobacco is sort of one giant microbiology experiment.

Other fungal toxins known to be produced by aspergillus and penicillium species include penicillic acid, which has been shown to bind to DNA and cause DNA breaks; and there's a new fungal toxin, which is sort of on the horizon, called gliotoxin, which kills CD4 cells and causes oxidative stress.

You may have noticed at the beginning of this talk that I originally gave this talk back in

2000. R.J. Reynolds sponsored me. We lost a whole decade here, for reasons that aren't quite clear to me, other than the political lack of willpower to get this legislation passed, the enabling FDA legislation. The World Health Organization seeks to regulate toxin levels on tobacco products. You notice here it was 2003. It's 2010; we're still not there yet.

Aflatoxin and mycocontamination of tobacco are prime candidates for a harm reduction strategy. I was very hopeful back in 2000; 2010 couldn't come soon enough.

That's the end of my talk.

Any questions? Thank you very much.

DR. HATSUKAMI: Any questions from the committee members?

Yes, Dr. Heck?

DR. HECK: Yes. I'd be interested in seeing the referenced support, citation support, for your statement that aflatoxin has been identified in environmental tobacco smoke. I looked into that myself some years ago and could not find support in the literature for that.

DR. LANE: The one thing that comes off the top of my head was internal documents that I was able to get off the internet as a result of the extensive litigation against the tobacco companies. In 1968, a group from the Wisconsin Alumni Research Foundation did smoke studies with tobacco and aflatoxin. That's where they found 100 percent carryover.

DR. HECK: I would certainly like to look at that closely because I looked into this some years ago and did not find substantiation for that in my own literature review.

Another comment. The statement that aflatoxin, or aflatoxin B1 in particular, is thermo-stable is accompanied by a statement that it decomposes at, what, 200-some degrees.

The temperature of a burning cigarette is about 1000 degrees, and there have been a couple peer-reviewed published studies of aflatoxin-doped cigarettes, looking at the smoke transfer. And my recollection of those studies is the effective transfer was essentially zero because the aflatoxin B1 was decomposed entirely.

I don't know if you're familiar with literature that I'm not, but that's the peer-reviewed literature that I'd seen.

DR. LANE: The one article that comes off the top of my head was research done at the Patel Institute back in the early '70s, where they looked at the combustion temperature of an idling cigarette, and it was 4- or 500 degrees Fahrenheit. I think it may explain why aflatoxin may come out in secondhand smoke, as the combustion temperature is much lower than primary smoke; you're not puffing hard on the cigarette.

DR. HECK: Again, I would have to examine that myself to develop a confidence that that analysis is substantive.

Just a broad comment. It's probably a little more than we want to get into here, but with regard to the mutation pattern seen in lung tumors, for instance, I think there's been a tendency in the literature, as well as in some analyses, to refer to that as a mutation spectrum. I would suggest to the committee that the term "spectrum" is probably not quite accurate in terms of p53 patterns seen in mature tumors because a frank tumor or tumor specimen is a product of many generations of cell selection. And we do see these hot spots or mutations selected for by, indeed, the effects of damage to that p53 gene that results in the continued division of the tumor cell.

So I think it can be misleading sometimes to look at the mutation pattern in a mature tumor and conclude upstream that the points of mutation do indeed coincide with hot spots for binding of different adducting species of DNA, for instance, the codon 249 mutation that's characteristic of aflatoxin.

DR. HATSUKAMI: Thank you.

Yes, Dr. Hecht?

DR. HECHT: I didn't see much in the literature on levels of aflatoxin in tobacco or cigarette smoke. In fact, I don't think there's anything.

DR. LANE: Yes. It's curious. It's the most potent carcinogen known, yet there's very little research done on it, which is kind of surprising.

DR. HECHT: So is it that nobody's analyzed it or is it that they analyzed it and they didn't find it; therefore, it wasn't published?

DR. LANE: The only thing I can comment is the gentleman who discovered aflatoxin in 1960 as recently as 2006 was a defense witness for the tobacco companies in the United States Department of Justice trial against tobacco companies, who got them on 152 counts of racketeering.

If you look back at the tobacco industry documents in the late '60s, they were very concerned about aflatoxin. And I think it's sort of damning that there aren't any scientists investigating this today.

DR. HATSUKAMI: Dr. Heck?

DR. HECK: Just a comment on that characterization. There has indeed been a considerable amount of research on aflatoxin, aflatoxin survival of the pyrolysis process. And to Dr. Hecht's point, there has not been, to my knowledge, documentation of the survival of aflatoxin in the burning process.

So there is some amount of that has been seen in the peer-reviewed literature. And I would suggest that if the company -- or if the committee develops an interest in this, we do refer to the peer-reviewed literature primarily as our scientific resources.

DR. HATSUKAMI: Any other questions?

[No response.]

DR. HATSUKAMI: Thank you, Dr. Lane.

Next on our agenda --

[Pause]

DR. HATSUKAMI: A change on the agenda. We're going to have a presentation, I believe, by the FDA, or maybe the CDC, on some of the criteria that have been used to identify a constituent as carcinogenic. So we'll go ahead and do that first.

[Pause]

DR. HATSUKAMI: We are going to take a five-minute break so we can prepare for the presentation. So stretch your legs and come back in about five minutes.

(Whereupon, a recess was taken.)

DR. HATSUKAMI: All right. I think if you can take your seats, we're ready to roll.

Based upon Dr. Burns' excellent suggestion, we are going to go over the carcinogen classification criteria so that we can all be in agreement. We're just going to confirm that we approve of this criteria.

DR. RICHTER: Does everyone around the table have a copy of the slides? Yes? Good.

So we've quickly pulled together information on the process that different organizations use to classify chemicals as carcinogens. And we've assembled information from the International Agency for Research on Cancer; the National Toxicology Program, which is run out of the National Institutes for Environmental Health Sciences at the National Toxicology Program; and also a brief summary of what's conducted at EPA, and Jennifer may want to add to that information.

Beginning with the National Toxicology Program, as noted in this slide, several agencies participate in the process. So it considers input not only from the National Institutes of Health, but also from the Food and Drug Administration and the CDC, as deemed relevant for any particular chemical that's being evaluated. I believe it's mandated by law that in the United States, the National Toxicology Program is required to release the Report on Carcinogens every two years. The current version is the 11th report, and the 12th report is under preparation right now.

The Report on Carcinogens restricts itself to identifying two groups of agents, known to be human carcinogens, and reasonably anticipated to be human carcinogens. And this distinction is going to be important when we look at the other groups.

The Report on Carcinogens does not list a substance that's been studied and found not to be a carcinogen, so there is no accompanying list that says, this was reviewed and the evidence is not sufficient to indicate it as a carcinogen.

The highest level of classification at the National Toxicology Program is what's considered clear evidence of carcinogenic activity. And this is based on any of these possible combinations, where they're looking for a dose/response relationship. And that would be either in an increase in malignant neoplasms in an animal study, an increase in a combination of both malignant and benign neoplasms, or a marked increase in benign neoplasm, showing evidence that it would progress to malignancy.

The second highest level is some evidence of carcinogenic activity. And this is again looking at animal data. So they would look for a chemically-related increase in neoplasms, which in this case can combine or separate both malignant and benign lesions. And the strength of evidence response is less than that required for clear evidence.

Then the third level is showing equivocal evidence, where there's a marginal increase of neoplasms that may be chemically related, perhaps not showing as strong a dose/response relationship.

The final two categories allow for the opportunity to show that there is either no evidence of carcinogenic activity or there's inadequate evidence. And the inadequate evidence of activity is distinguished from equivocal in that there are major qualitative or quantitative limitations that allow correct interpretation or show enough evidence for a carcinogen designation.

The International Agency for Research on Cancer has evaluated, as you can see, a large number of carcinogenic compounds over many decades. They have a well-defined classification system, which is different from the National Toxicology Program system in that it allows not only a classification of carcinogenic to humans, probably carcinogenic and possibly carcinogenic, but they also have group 3, which is unclassifiable, or group 4, probably not carcinogenic to humans.

Periodically, the International Agency for Research on Cancer will reevaluate a chemical, perhaps based on new evidence, new studies that have been produced, something that indicates that there's mechanistic data available that will allow the group to reevaluate. So it is possible for a chemical that is classified in one way to be reevaluated over time and the classification to change.

The highest level of carcinogen classification at IARC is sufficient evidence, and that's indicating a causal relationship between exposure and outcome. Limited evidence suggests a positive association, and there's credible evidence that there is a causal interpretation of the results.

Inadequate evidence is that there are available studies, and there are insufficient quality or consistency or power in an epidemiological design to assess a causal relationship.

The final category of looking at the human carcinogenicity data is to determine that there's a lack of carcinogenicity. And that's important because it's requiring an adequate study to make that assessment in terms of design and statistical power.

IARC also considers animal data in their assessment of carcinogenicity. And again, as with the human data, the highest level is sufficient evidence, with a causal relationship between exposure and disease outcome; limited evidence, again, data suggestive of carcinogenic effect; inadequate evidence that the available studies are insufficient, and that could be for numerous reasons, perhaps not enough animals in the study design or the dose selection was not appropriate; or that last category of lack of carcinogenicity, where there has been an adequately designed and conducted study that fails to show a tumor incidence increase in at least two species over background -- or, excuse me, over control.

We were able to also identify some of the information that IARC considers in their deliberations, and that's regarding mechanistic data. We've had some discussion of that this morning, about mechanisms underlying disease outcome. Their deliberations may include data on preneoplastic lesions; tumor pathology; genetic effects; structure/activity relationships, especially as it may relate to mutagenicity; metabolism and toxicokinetics; and the physical/chemical parameters of the chemical in question.

Based on the human and the animal data, IARC arrives at one of five possible classifications, the highest being group 1, where there's sufficient data in both humans or animals; and in the case of when there are only animal data, they look for supporting, strong mechanistic data in humans.

Group 2A also requires evidence in humans and animals, although it may be limited in humans and sufficient in animals; group 2B, limited evidence in humans, and less that sufficient evidence in animals; group 3, inadequate in humans and inadequate or limited in animals; and group 4, lack of carcinogenicity.

The U.S. Environmental Protection Agency maintains the Integrated Risk Information System, referred to as IRIS. And the IRIS database maintains a summary of the chemical evaluations that the Environmental Protection Agency conducts to arrive at the derivation of both reference concentrations, RFCs, and reference dose, RFDs, for environmental pollutants.

With respect to carcinogenicity, they also employ a rating system, and it's very similar to the others in that they look for data both in humans and animals, group A being carcinogenic to humans; group B, likely to be carcinogenic to humans; group C, suggestive evidence of carcinogenic potential; group D, inadequate information; and group E, not likely to be carcinogenic to humans. So slightly different wording than what IARC uses.

EPA states that their classification criteria is based on a weight of evidence approach. And similar to the other groups, National Toxicology Program and IARC, they include both epidemiological data and animal data. And they also consider some of the supporting mechanistic considerations, including physical/chemical properties, structure/activity relationships, comparative metabolism, and toxicokinetics and mode of action.

One other group that's been mentioned this morning is the California Environmental Protection Agency. And as has been stated, they have a process employing qualified experts at the state level to review both human and animal data to arrive at designations of carcinogen or reproductive toxicant.

They have basically used a process of identifying recommendations from the state experts, and then looking for identification of other authoritative bodies such as the national U.S. Environmental Protection Agency, the Food and Drug

Administration, IARC, NTP, and others. And they conduct their activities under the requirement by state law that they can label these chemicals, for regulatory purposes, as carcinogens or reproductive toxicants.

DR. HATSUKAMI: Thank you, Patricia.

Any questions from the committee?

[No response.]

DR. HATSUKAMI: No questions? So I believe what we did this morning was to adopt the criteria that has been used by IARC, as well as the NTP.

So are there any concerns about adopting these criteria to identify our carcinogens? Yes?

DR. HECK: I do think, Pat, you've done a nice job of summarizing the classifying schemes that have been done for different purposes by these different groups.

I have one concern with regard to the NTP classification scheme, and that is, we know now from experience that the NTP testing paradigm, wherein two species of rodents are tested at one-half the maximum tolerated dose for their lifetime, we've learned now from that experience -- and this is something that our field of toxicology has been wrestling with in recent decades -- that about 50 percent of all chemicals known to mankind, 50 percent of drugs in the PDR, around 50 percent of agrochemicals, about 50 percent of food additives in grass materials, and perhaps 50 percent of botanical chemicals found in tobacco, might reasonably be anticipated to be carcinogens by the NTP's testing process.

So I think the IARC process and I think the EPA process probably are the more thoughtful sort of evaluations that, if it comes down to that, that this group might consider or wait, as opposed to the NTP's process.

DR. HATSUKAMI: Dr. Hecht?

DR. HECHT: The Report on Carcinogens does not only consider the results of the NTP bioassays, but it considers all the data, including epidemiology data and including other animal data that may have been generated outside of the NTP. It also includes data on occurrence and mechanistic data. So I think it's not quite correct, what you said. And I think you would see, if you look at the Report on Carcinogens, in general, quite an agreement between their evaluations and those of IARC.

DR. HECK: Thank you for that clarification. I would agree with your statement here, and I do think that sort of thoughtful process, as opposed to, for some of these materials that we may be considering here, we're going to see positive NTP bioassay results. And those should be weighed in the context of the other available information from epidemiology and mechanistic studies, as is done in the Report on Carcinogens or by IARC.

DR. HATSUKAMI: Dr. Burns?

DR. BURNS: Well, again, I would think it would be a fairly simple process to identify, on the list that we've already got, items that are not carcinogens, that have not been assessed as carcinogens by IARC but are by some of the other agencies. And we could think that through in a fairly limited basis.

I'm not sure that -- from what I remember this morning, almost all of the compounds were ones that IARC had assessed as 2A or 2B or higher. And so if there are some, then it certainly would be useful to take a look at them.

DR. HATSUKAMI: Ms. Jinot?

MS. JINOT: Yes. I had a question about phenol in that regard because I don't think it's classified by any of those, by EPA or NTP or IARC, as a carcinogen. In this sheet that was with our materials on example constituents and their potential associations, it says that phenol is a tumor promoter based on ATSDR, and Hoffmann and Hoffmann, and Butwell (phonetic) and Bartsch (phonetic).

So to include that, are we going to provide other criteria, or how are we rationalizing putting that on the list, I guess?

DR. HATSUKAMI: That's a really good point.

Yes, Dr. Farone?

DR. FARONE: In the work that we do, it's a precursor for catechol, next oxidation product of phenol. Environmentally, we find that they go together so that -- I mean, in and of itself, I don't think it matters. But it is associated, at least from what we've seen environmentally, with catechol.

MS. JINOT: Right. And there are other effects, too. So I guess another question is -- because I think the respiratory effects and things are established. So I guess to what extent do we have to break these down into the different categories, or as long as we're fairly sure of one of the types of effects, shall we just include it in the list, or do we have to be fairly certain of each of the types of effects that we want to list it for?

DR. HATSUKAMI: Well, that's really up to the committee to decide. But I think the FDA wants a list of the potentially harmful and harmful constituents. And it's for the committee to decide. And certainly, we need rationale for each of the constituents that we include.

DR. BURNS: And the first time it's included, we need to have a criteria for its inclusion.

DR. HATSUKAMI: Right. Yes.

DR. BURNS: So we put phenol on the list as a carcinogen, and if phenol is not carcinogenic, then it should come off until we assess whether it should be on the list for other reasons.

DR. HECHT: It's not a carcinogen and it's not a tumor promoter, so it shouldn't be on the list.

DR. BURNS: I know. But Dietrich liked it.

DR. HECHT: What's that?

DR. BURNS: Dietrich used to like it.

DR. HECHT: No. Actually, Dietrich didn't like it.

DR. HATSUKAMI: So it sounds look the committee thinks that the phenol should be taken off the list as a carcinogen. Yes.

Any other additional comments or?

Yes, Rich?

DR. O'CONNOR: Just more of a general question of the extent to which the different lists agree with one another, so the extent to which -- if IARC and NTP have evaluated a component that we have identified as in tobacco smoke, to what extent do they both agree that they're definitely carcinogens or probably carcinogens? And to what extent, then, if they don't agree, which way do we fall, and does that matter?

DR. HECHT: I don't know the answer to that offhand, but I think there's pretty good agreement. And the Report on Carcinogens criteria are slightly different because their top category is "reasonably anticipated to be a human carcinogen," whereas IARC says it is a human carcinogen. So there's a nuanced difference there. And I think if you look through them, you'll find that the ROC may have a number of examples where it's reasonably anticipated to be a human carcinogen, where IARC would have it in 2A.

DR. HATSUKAMI: Ms. Jinot?

MS. JINOT: Right. I think they do largely agree, except sometimes where they don't is because they were done at different points of time, so slightly different databases. And I think that we would be justified in taking it as long as it's on one of those lists.

DR. HATSUKAMI: Dr. Farone?

DR. FARONE: Yes. When they don't agree, I think that's where you look at other criteria, or you say, okay, I give benefit of the doubt, and then see how deeply we feel about it with regard to tobacco and tobacco smoke as being relevant to what it is. Because if it's on one list but not the other, and it's present at a fairly large extent in smoke, then it may warrant being on the list for concern of potential harmful, at least.

DR. HATSUKAMI: Any other comments?

[No response.]

DR. HATSUKAMI: So just to summarize, it seems like the criteria that we are going to be using is predominately based upon the IARC criteria, but we will also be using some of the criteria from the EPA as well as NTP.

Am I correct?

[Affirmative nods from committee members.]

DR. HATSUKAMI: I just wanted to make sure that we were clear on that.

[Question posed by staff.]

DR. HATSUKAMI: Well, let's ask the committee.

Would the committee like to review the list of carcinogens prior to the time we hear from

Dr. Watson? And then after his presentation -- not tonight, but tomorrow -- we'll be going over whether there are assay methods for the carcinogens that we identified.

So would any of the committee members want to go over the list again or should we just go ahead and have Dr. Watson speak?

Yes, Dr. Burns?

DR. BURNS: I think it doesn't make much sense to go over the list as a list at this moment. What might be useful would be to take that list, and then add a column as to whether it's on the IARC list. And then for the ones that -- if they're not on an IARC list, what list are they on.

DR. HATSUKAMI: Good point.

DR. BURNS: So that we have a clear document that describes how they got onto the category.

DR. HATSUKAMI: So maybe --

DR. BURNS: I don't think we necessarily need to look at every, single one of them in each list. But we've said that IARC is the primary category, and only for ones that aren't on the IARC list would you list the others.

DR. HATSUKAMI: That's a good point.

So maybe that's something that we can do tonight, and then have that available to us tomorrow.

So with that, I think we should go ahead and proceed with Dr. Watson's presentation, and then we'll adjourn for the day.

[Brief pause.]

DR. WATSON: Hello. My name is Cliff Watson. I'm a research chemist at the Centers for Disease Control and Prevention in Atlanta, Georgia.

I'll deviate here just for a second. I'd like to thank the previous speakers, particularly Dr. Higby, who raised valid concerns about testing and testing methodologies, as well as the very excellent presentation by Dr. Ogden, who also touched on some of this, sources of analytical variability. These will be decisions that will feed into the various methodologies and strategies that FDA needs to consider in terms of asking for constituent reporting.

That's not really the focus of my talk today. Really, as a chemist, my charge here today is to go through the example list, talk about some of the common analytical methodologies that are commonly employed -- this by no way is going to be an exhaustive review, but is a basis for laying the groundwork for some of the work that's coming up, when we get into the nitty-gritty of what compounds do we want to look at, how we're going to look at them, how we're going to generate them.

I really want to lay the groundwork here, and just plant the seeds in your mind of things we need to think about, and define some of the common terms and some of the common abbreviations that we'll be bandying about quite a bit. For those of you that are not chemists, and we're talking all these acronyms, it may be helpful to at least have seen them once before.

So the objectives of my talk today are to touch on several points here. I'd like to look at some readily available sources of pertinent analytical methods; identify some common terms, abbreviations, and a general overview of an analytical procedure, for those of you that don't work in this area.

The bulk of my presentation will review some of the commonly used methods for measuring specific chemicals, and ones that sort of fit together neatly, and where you can benefit by analyzing multiple compounds with a particular analytical method.

Then finally, as you see in my presentation, there are multiple methods that have been proposed or used or studied, and how do we address the situation where there might be more than one acceptable method, an analytically acceptable method, that is. And then we'll wrap up with a summary.

This slide summarizes some of the various sources for analytical methodologies that discuss harmful and potentially harmful constituents in tobacco or tobacco smoke. And you can see from this list, there's a range of methods available, from the ISO methods, the recommended methods from CORESTA, from various governmental agencies, commercial laboratories, the tobacco industry.

There are tons of -- we've discussed today examples of methods in the peer-reviewed literature. There are too many to mention. And again, the point of today's talk is not really to provide a detailed overview for each one of the methods, but really just sort of hit some of the highlights and set the groundwork for future discussions.

I gave you the purpose of today's presentation. I'd just like to define a couple of terms here. Method, and what I'm referring to here really is an analytical method, is a standardized procedure to measure the amount or concentration of a specific chemical or group of chemicals. And this could be -- for instance, the specific chemical could be a benzene. A group of chemicals could be tar, or it could be a group of polycyclic aromatic hydrocarbons.

An analyte, again, is what we're measuring, and so that's what we're trying to determine. And whether that's benzene or toluene, I'm going to use the term analyte sort of as a generic term which could refer either to a specific chemical or to a mixture of chemicals. I think it'll be obvious as we're going through.

To just reiterate again, the methods I'll mention here are not an exhaustive listing by any means, and were simply picked as typical examples. Mention of a specific method or source of a method is in no way to be considered an endorsement of that method in any way, shape, or form. And really, these were chosen for convenience to serve, really, just as illustrative examples.

Perhaps the most fundamental outline of an analytical procedure is shown here. And today we'll concern ourselves with how the sample analysis is done, not so much how the sample was generated. This, I think, we need to leave for a separate meeting because that'll be dependent somewhat on the list of compounds that we pick.

In general, most times a chemist will be presented with a complex analytical mixture -- and we've talked about this today in tobacco and tobacco smoke, where we have thousands of compounds that are present -- and we need a way to sort those compounds out to make it easier to analyze them. And a typical first step is to do some sort of separation. In the analytical instrumentation realm, there are several ways this might be done. These are some of the more common ways, using gas chromatography, HPLC, ion chromatography.

What these, for those of you that aren't chemists -- and you may have seen CSI or one of these TV shows where they show this black box, and they walk up to it and it spits out the results right away? That's not quite how it works. There's a little bit more to it than that.

But in general, these things I've listed in separation are sort of black boxes. You inject a sample into it, and by some way, shape, or form, they try to separate those into things that are easier to analyze. Then we have the detection scheme. And we're going to do quantitative detections; obviously, we want to measure levels. And there's a variety of ways this can be done.

There are some detectors that are so-called universal detectors, in that basically they detect everything. And so it relies heavily on the separation to resolve the compounds to detect, then some of the detectors are more chemical-selective, like a mass spectrometer, which basically does detection based on the chemical structure and gives you a structure of specific information so you have more confidence in your measurement.

We're now going to go through a whole series of tables like this one. And I apologize for those of you that work in this area; this will be a very simplified version of these data in their presentation here today. But for the uninitiated, hopefully these slides will serve an illustrative point or two I'd like to make here.

One of the most common methods employed for analysis of tobacco smoke is the so-called TNCO method. TNCO stands for tar, nicotine, and carbon monoxide. The reference I've shown here at the bottom, one of them is the Health Canada method. And one interesting point I wanted to make here is this Health Canada method is built on a series of ISO methods. And so for these various analytical methods that are out there, many of them are contingent or built upon previously established, valid analytical methods. This isn't always the case, but it happens to work out in this particular case.

A couple other interesting points. There's more than one way to analyze a particular chemical and a complex mixture. The typical way for analyzing nicotine, for instance, is using a gas chromatography device with a flame ionization detector, an FID. This is a relatively inexpensive piece of equipment. One could also run the same ample on a GC/MS, which is a more complicated, more expensive piece of equipment, but it, in many cases, serves the same purpose.

In the normal TNCO, water's included. Water's important because water has to be accounted for in the determination of tar. I know most people in this room probably know what tar is. But tar is basically the total particulate matter less the water and nicotine content.

Going through our example list, I've tried to group the chemicals as best I could in terms of their chemical or physical properties where they're normally analyzed together as a group because they're amenable for a particular method. These particular compounds are all referred to as volatile organic compounds. They generally have high vapor pressure, and they are often routinely analyzed by a GC/MS approach.

These chemicals are generally referred to as carbonyls because of their chemical structures. And as you can see, they're amenable to analysis by more than one analytical technique. And much work has been done on these and many of the other chemicals I'll mention today. So please keep in mind, as I previouslytated, the two references shown here are only for illustrative purposes, and they by no means represent the vast amount of work that's been done in this area. There are tons of publications and other methods that are available for looking at these.

Again, the point I wanted to make here is there is more than one way to analyze these types of compounds. Again, you can see they can be analyzed by HPLC with UV, which is a spectrometric detector. Again, that's more of a universal detector, although it does offer some chemical specificity; as well as the GC/MS method we mentioned before.

Here we have the so-called phenols. And

these chemicals generally can be analyzed by the similar method due to their chemical similarity, so they're analyzed by the same method.

These are an example of compounds that are often referred to as semi-volatiles. And often, to improve their detection -- because they are semi-volatile -- they have to be derivatized. And this is an extra step that has to be done to enhance their detection. Generally, as a chemist, one wants to have the simplest procedure possible to give the highest quality data possible. And so when we have to think about things like derivatization; it throws an extra wrinkle in there. But again, it's good to be aware of what sort of caveats are available for which methods or weighing one method against another. It's one criteria; how much complexity does it take to do the sample workup?

The nitrosamines, we've discussed these quite a bit today. Historically, these have been analyzed by a thermal energy analyzer. I think many labs around the world still use TEA. Most modern laboratories, at least analytical laboratories, I believe, are using HPLC with tandem mass spec. That's just abbreviated here by MS/MS.

A GC/MS can be used. But I think the more common procedure these days is using the HPLC tandem aspect. Again, there are tradeoffs between these two methods in terms of the kind of information you get out there, as well as the costs and complexity of operating and maintaining these instruments.

The methods I've sort of just combined all here in one big table. They may or may not be amenable to analysis together; it depends on the method. The variety of type of methods that are normally used for these are some sort of photospectrometric absorption or emission detector or they're analyzed in combination with an inductively coupled plasma interface to a photospectrometer detection scheme or to a mass spectrometry detection scheme.

Here are some different means. I've sort of grouped these together, although rightfully, the pyridine and quinoline are slightly different from the ones above. They're slightly a different class of compounds. But the bottom line is that they're all volatile. They're all amenable to analysis by a GC mass spec technique, as well as other techniques.

The minor alkaloids, so these are chemicals that are related to nicotine. And the term "minor" is used to distinguish them from the predominate alkaloid, which is nicotine in tobacco. And these chemicals are readily analyzed by GC mass spec as well as other techniques.

It's getting harder now to group these chemicals together based on the chemical/physical properties. So on this and the next table, these chemicals are just listed together for convenience, and don't particularly share much in terms of chemical similarities in order to group them together as before.

As you can see, there are a variety of analytical methods that can be used for their analysis, ranging from HPLC/UV analysis to ion chromatography, GC/MS, chemiluminescence. And it really depends on the type of compound as to which particular assay may or may not be suitable for their analysis.

This is the final example here. I appreciate you guys bearing with me as we go through this initial example list. And again, this just summarizes the chemicals that are remaining. The top three chemicals, glycerol, propylene glycol, and triethylene glycol, typically these are humectants. They probably can be analyzed in the same type of analytical method. Typically, one could use a GC with a flame ionization detector and mass spectrometer for their detection.

Benzo[a]pyrene we've discussed before. It's been extensively studied, and used as a marker for other polycyclic aromatic hydrocarbons. One could measure these by simply HPLC. One could also do a much more extensive measurement using HPLC combined with a mass spectrometer for detection. And you could easily add many of the other polycyclic aromatic hydrocarbons to the same sort of method. You can get a battery of results, more bang for your buck, from one particular method.

The other chemicals, again, there are a

variety of ways they can be analyzed, either in the tobacco products or in tobacco smoke. You can see there's a variety of methods there that are commonly used.

So I've gone through here and I've sort of pointed out the cases where there are multiple analytical methodologies that exist. Some of these methodologies are amenable to analyzing a class of compounds, chemicals that are related in terms of physical properties or chemical structure.

Oftentimes, there's more than one analytical method available for analyzing them. And so is it possible that we can have different methods that can provide comparable results?

There are ways to achieve this. This was touched upon a little bit in the earlier studies. From a different perspective, looking at this between intra- and inter-laboratory comparisons, what I'm really talking about here is an inter-laboratory comparison, particularly if you're having to make decisions on economy of scale, of analyzing a particular class of compounds versus another, if you're a large company that has a bigger program. A smaller company, there may be tradeoffs you need to consider. There may be different approaches that are possible.

Traditionally, how one establishes equivalency between methods is that you select a representative set of samples for comparison, you do your analytical determination, and then you apply a very statistical test to compare the results to see whether or not they're equivalent.

Here are some considerations for selecting a specific analytical method. The first, by far, is applicability. And again, this was touched on by the earlier talks this morning. Is the method suitable for job we need done? And what is its range of suitability in terms of what is the precision you can get out of that method? These are some of the topics that were talked about, Dr. Higby and Dr. Ogden this morning, and how one addresses these.

I don't want to really get sidetracked on this issue right now because I think we need to get a little further along in the process before you start zeroing in on specific methods that might be useful for these classes of compounds.

There are other things one can discuss in terms of look at different methods. It's the requirements in terms of sensitivity, specificity, analytical figure of merit, that help determine a particular method's suitability. And again, these all sort of feed back into the applicability; is a particular method applicable for a particular task.

So in summary, as we've seen, there are variety of methods, analytical methods, currently available that can analyze a range of compounds, either in tobacco products or in tobacco smoke. In many cases, there's more than one method available or methodology available, analytical technique available.

There are agreed-upon scientifically valid ways for comparing methods and for making selection criteria in terms of how suitable a method is for a particular task. And hopefully, I've made those points clear today.

Thank you for your attention, and I'd be happy to try to provide answers to any clarifying questions.

DR. HATSUKAMI: Thank you, Dr. Watson.

Dr. Farone?

DR. FARONE: This may be a question on just -- it was mentioned this morning something about something being plus or minus 50 percent. And it sounds good to me. If the target is 10 nanograms and you're measuring 2, plus or minus 50 percent is below 10, so that's what you need to know.

Could you make some comments about the levels of the analysis and acceptable variation in tests, say, compared to something that's maybe down near the detection limit for the instrument versus something that's way away from it? In other words, what I'm getting at here is, the variability in the numbers that you get may seem large, but they still may be okay for the purpose of defining whether things are different than some standard or greatly different from one to another.

DR. WATSON: That's a little bit outside of my area of expertise, and so I don't want to speak out of school, so to speak.

The point you raise is very valid. And this is up to the subcommittee as well as the full committee and then ultimately FDA's decision as to what they want to do, if they want to establish ranges. My understanding of your question is if you have a range that's set up here and then you have a number you measure down here, and that number is plus or minus 50 percent, that might serve a useful purpose.

There have been several recent publications that have come out that have looked at inter-laboratory comparisons, looking at the Hoffmann list. There was a really nice publication that came out in 2009. I think one of the interesting points to me that was raised in that publication is that the confidence in your measurement can be chemical-specific, either because of the nature of how the thing is generated or the nature of the measurement, and that we need to be cognizant of this. You just don't want to blindly establish guidelines; you want to have guidelines that make sense in terms that the numbers that you measure are meaningful.

DR. HATSUKAMI: Dr. Lauterbach?

DR. LAUTERBACH: I'd like to make more of a comment than a question.

First, Dr. Watson, thank you for that very nice presentation. But I do think Dr. Watson's presentation gives us a very important message as we move forward. I noticed the citation for the menthol method. That menthol method in the literature would not fly in most tobacco companies because of the way menthol escapes from tobacco or cigarettes. There are some very good menthol measurements.

I think it's very important as we work forward here, and it was mentioned in the CITMA presentation this morning, that we basically have a joint tobacco industry/FDA methods development committee to go through some of these things because there's lots of tricks of the trade in doing tobacco and tobacco smoke analyses. These are not written down in the ISO methods. They were never part of the FTC methodology. And a lot of these things you don't know about until you start into a tobacco laboratory and learn from your coworkers and supervisors how to get the work done.

DR. HATSUKAMI: Any other comments?

Dr. Burns?

DR. BURNS: Cliff, that is a very nice run-through, and I just wanted to clear on a couple things that I think would be important.

When you list a whole series of chemicals of a similar type and say that they're all obtained by the same method, that means one run of that method gives you five metrics, one for each of the five compounds; is that correct?

DR. WATSON: That is correct.

DR. BURNS: So that it's not necessary to count that as five different tests, in a sense. It's five different outcomes of the same test.

DR. WATSON: That is true. For each one of those compounds, though, you'll establish statistical criteria about what's acceptable or not for the performance of that particular method.

DR. BURNS: Right.

DR. WATSON: But in terms of an economy of scale -- maybe I didn't make this really clear in the presentation, but that sort of implied it. But when you work in this area, you forget to make these points.

But yes. The beauty of some of the analytical capabilities are that you can measure, much like we were discussing PHs this morning, you can measure more than one representative chemical of that particular class in a method. You can't measure everything, as we've heard from the other people, because it's just too daunting. There's too much information. There's too much data. But you very easily can measure a series of chemicals that share either a physical similarity, in terms of their physical properties, or in their chemistry. And basically, in a particular method, you can measure multiple chemicals.

DR. BURNS: And at some point, it would be useful to have an assessment of how many methods would be required to measure the list that we come up with because, obviously, it will be far fewer methods than it will be lines on the particular list.

Secondly, the question that I think would be also useful to know would be, for the CDC lab that you're responsible for, how many of those methods are currently -- how many of the constituents that we are talking about are currently up and running as analyses that could be done at the CDC lab, where presumably we have already reasonably well-developed and described methods for actually accomplishing that, as well as quality control metrics for the measurements?

DR. WATSON: That's a difficult question. It seems straightforward on the surface. At the CDC, we have analytical methodologies for measuring -- I can't remember off the top of my head -- maybe 50 to 100 compounds. A lot of these are flavor compounds, so they're not really relevant to today's discussion.

DR. BURNS: Right.

DR. WATSON: But the difficulty comes in, in sort of defining the list of compounds. And from that list of compounds, once that's defined, then we have to define how we're going to generate the samples for those particular things.

There are standard smoking machine methodologies that have been used in the past, but it will be up to the recommendation of the committee, and I guess the final will be ultimately up to the FDA to decide exactly how we're going to generate that, how the samples are generated is going to affect how we make the measurements. And so you see the dilemma there, that basically we need to know what our task is exactly in order to say how easy or difficult it will be to make these measurements.

DR. BURNS: Well, but if the samples are adequate, and I understand that that's an issue that would have to be specified, it would be possible, at a subsequent meeting, for you and the CDC lab to provide the group with a statement about the number of the compounds on the list that the CDC has or could easily generate procedures for and analytic methodology descriptions for measurement of those. Because that will help us make the next leap, which is, if the CDC is not currently doing it, are there other laboratories for which there are established methodologies.

DR. WATSON: Right.

DR. BURNS: But I think the committee would be comfortable that if the CDC lab is currently doing it and currently has a methodologic description for how it can be done, that that's a clear statement that that methodology is available, is developed, and a reasonable assessment that that methodology is one that we can endorse as a committee going forward, as opposed to having to make some kind of independent judgment about the multiple different methodologies that might exist out there.

Because as I understand it, we do have to come up with some recommended method for each of the constituents that we propose.

Is that correct?

DR. HUSTEN: Method or methods.

DR. WATSON: You raise several interesting points. Yes, we could provide a list of things that we can analyze, that we do in our laboratory as part of our research efforts. There are a variety of other sources of methods, too, that currently exist.

I name three commercial laboratories on that list, and I name them because either they have their methods published on their websites or they have a list of their standard battery of tests that they can perform. So we could definitely compile a list of things that people routinely analyze.

To Dr. Hecht's point this morning -- basically, being a chemist, there's no challenge that I can't tackle. Methods can be developed for looking at some of these things.

As we were going through the list today and I was thinking in the back of my mind about the complexity of some of these things, there are some analytical challenges for analyzing some of these compounds, particularly if you want to go looking at radioactive compounds. That involves a whole new level of complexity in terms of being able to log samples and standards in the lab, tracking those, and making sure that our workers remain safe.

DR. BURNS: But it may make some sense to take, in the initial list of compounds that we're recommending, ones for which the methods are already developed and operational, and then reconsider in a year, when you've had an opportunity to develop these newer methods, the addition of compounds that are defined as potentially hazardous but aren't included on the original list because we don't have a methodology that can be clearly defined at this moment in time.

DR. WATSON: Yes.

DR. HATSUKAMI: Dr. Lauterbach and then Dr. Farone.

DR. LAUTERBACH: I just want to caution people, and I'm very pleased to see that the CDC is maybe heading toward its own laboratory to be sort of the gold standard for other smoke laboratories in the United States. But getting methods to work, and work reliably from laboratory to laboratory, and not having a great deal of what's called a reproducibility problem, in ISO standards, that's sort of ISO big R, which oftentimes is severalfold what a within-laboratory variation could be. It is basically the inter-laboratory variation that could be a major problem in getting our methods program forward.

DR. HATSUKAMI: Dr. Farone?

DR. FARONE: Yes. I am thinking of two different actual problems. The first is a method that can measure it. And that's an easier problem that a method that it's economical to measure lots quickly.

An example that comes to mind, you want to do metals in tobacco. If you grind up 10 grams and put it in energy-dispersive x-ray, you can get down to a couple ppm of all metals in one shot. Now, if that level isn't adequate for the purpose, like you need to know it more -- not more precisely, but you need to be more sensitive than that, then you may have to go to extraction, ICP/AA, which gets to be a much more expensive proposition.

So just coming up with a method to prove that it's there and it can be done is one thing. And to come up with methods that are economical, not just in money but in getting data that we want to get in a short period of time, is a different thing.

And I think both of those are important. But to establish that it can be done is probably the first requisite, and then to economize on doing it is probably the second.

DR. HATSUKAMI: Yes. Dr. Burns?

DR. BURNS: Yes. What I'm trying to avoid is the comments that have been made that what we really need to do is turn this over to ISO, and we'll have ISO develop an internationally standardized method for each one of these things, and that will be available some time in your grandchildren's lifetime.

I mean, if we're going to do anything with this process, we need to begin to operationalize the knowledge that we currently have and how we do this. And yes, I understand that there will be issues of comparisons across laboratories. There will be issues of standardization within laboratories. There will need to be some kind of quality assurance program to make sure that when you get a new laboratory tech, or the laboratory tech comes in with a hangover, you get valid data out of it. You've got to be able to rely on the information.

But those are relatively clear processes for the translation of a method from one laboratory to a multiple-laboratory process. That would have to be done, but there isn't any conceptual gap in our understanding of how you go about finding out whether a test that's done in one laboratory can be done with a reasonable confidence interval in a set of four or five laboratories around the United States. That's something that we know how to do, and is a fairly appropriate methodology.

What I'm concerned about is that we don't put in place barriers that say, well, you know, yes, we know how to measure this, but I don't know whether we can make any measurements because we haven't worked out all of these details. If we have a methodology that people feel gives sufficient precision and that can be implemented at reasonable cost and efficiency, then I think we have something that we can recommend to the parent committee that has to -- any process that they roll out and go forward with will have to assess the question of how do you get an adequate sample of cigarettes, how do you test it, how do you compare testing across laboratories so that you know the results are comparable and all of the rest.

DR. HATSUKAMI: Any additional comments?

DR. LAUTERBACH: I just think that we have to be very careful on this, Dr. Burns. We certainly don't want to take shortcuts for the sake of taking shortcuts. Even on the validation of chemical methods for pharmaceuticals, a number of steps have to be taking place. And I don't see us recommending anything less for these test methods.

All the standard-setting organizations, such as ASTM, International, ISO, have very well-defined criteria for doing method validation. And that was basically those criteria learned over the years from people having problems and not being able to get the same results among qualified laboratories. Going to the smoking laboratory is a very chancy experience, and many times you don't come out with the desired results.

DR. HATSUKAMI: I think we'll end with those comments.

So what I want to do -- we've done a lot of work. I want to thank the presenters today; they did an excellent job in terms of informing us and helping us in our deliberations. And I also want to thank the committee members and consultants as well. I think we've made some good progress related to our charge.

Before we adjourn, I have to make a few

comments. Committee members and consultants, please remember that there must be no discussion of the meeting topic this evening, either amongst yourselves, with the press, or with any member of the audience. So thank you.

We will convene again tomorrow morning in this room at 8:30 -- oh, sorry, 8:00 a.m. Please take your personal belongings that you may want with you at this time.

So thank you, and we will see you tomorrow morning at 8:00.

[Whereupon, at 4:49 p.m., the meeting was adjourned.]